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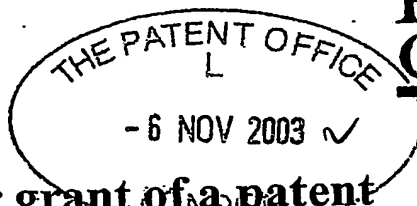
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1/77

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1. Your reference

46852.GB01/JMD

2. Patent application number
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0325956.1 ✓

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Addex Pharmaceuticals SA
12 Chemin des Aulx
1228 Plan-les-Ouates
Geneva
SWITZERLAND

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of incorporation

SWITZERLAND

8578799 001

4. Title of the invention

Novel Compounds

5. Full name, address and postcode in the United Kingdom to which all correspondence relating to this form and translation should be sent

Reddie & Grose
16 Theobalds Road
LONDON
WC1X 8PL

Patents ADP number (if you know it)

91001 ✓

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application
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Date of filing
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Number of earlier application

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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:
a) any applicant named in part 3 is not an inventor,
or
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Description	82
Claim(s)	12
Abstract	1 <i>DL</i>
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11.

I/We request the grant of a patent on the basis of this application.

Signature

Date

6 November 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

J M DAVIES
01223 360350

Warning

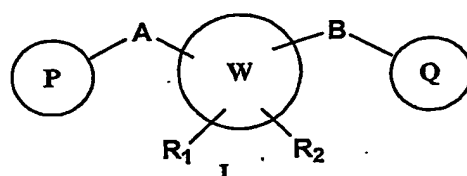
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NOVEL COMPOUNDS

FIELD OF THE INVENTION



The present invention provides new compounds of formula I as modulators of metabotropic receptors – subtype 5 (“mGluR5”) which are useful for the treatment central nervous system disorders such as for example, cognitive decline, both positive and negative symptoms in schizophrenia as well as other disorders modulated by mGluR5 receptors

BACKGROUND OF THE INVENTION

Glutamate, the major amino-acid transmitter in the mammalian central nervous system (CNS), mediates excitatory synaptic neurotransmission through the activation of ionotropic glutamate receptors receptor-channels (iGluRs, namely NMDA, AMPA and kainate) and metabotropic glutamate receptors (mGluRs). iGluRs are responsible for fast excitatory transmission (Nakanishi S et al., (1998) *Brain Res Brain Res Rev.*, 26:230-235) while mGluRs have a more modulatory role that contributes to the fine-tuning of synaptic efficacy. Glutamate performs numerous physiological functions such as long-term potentiation (LTP), a process believed to underlie learning and memory but also cardiovascular regulation, sensory perception, and the development of synaptic plasticity. In addition, glutamate plays an important role in the pathophysiology of different neurological and psychiatric diseases, especially when an imbalance in glutamatergic neurotransmission occurs.

The mGluRs are seven-transmembrane G protein-coupled receptors. The eight members of the family are classified into three groups (Groups I, II & III) according to their sequence homology and pharmacological properties (Schoepp DD et al. (1999) *Neuropharmacology*, 38:1431-1476). Activation of mGluRs lead to a large variety of intracellular responses and activation of different transductional cascades. Among mGluR members, the mGluR5 subtype is of high interest for counterbalancing the deficit or excesses of neurotransmission in neuropsychiatric diseases. mGluR5 belongs to Group I and its activation initiates cellular responses through G-protein mediated mechanisms. mGluR5 is coupled to phospholipase C and stimulates phosphoinositide hydrolysis and intracellular calcium mobilization.

mGluR5 proteins have been demonstrated to be localized in post-synaptic elements adjacent to the post-synaptic density (Lujan R et al. (1996) *Eur J Neurosci.* 8:1488-500; Lujan R et al. (1997) *J Chem Neuroanat.*, 13:219-41) and are rarely detected in the pre-synaptic elements (Romano C et al. (1995) *J Comp Neurol.* 355:455-69). mGluR5 receptors can therefore modify the post-synaptic responses to neurotransmitter or regulate neurotransmitter release.

In the CNS, mGluR5 receptors are abundant mainly throughout cortex, hippocampus, caudate-putamen and nucleus accumbens. As these brain areas have been shown to be involved in emotion, motivational processes and in numerous aspects of cognitive function, mGluR5 modulators are predicted to be of therapeutic interest.

A variety of potential clinical indications have been suggested to be targets for the development of subtype selective mGluR modulators. These include epilepsy, neuropathic and inflammatory pain, numerous psychiatric disorders (eg anxiety and schizophrenia), movement disorders (eg Parkinson disease), neuroprotection (stroke and head injury), migraine and addiction/drug dependency (for reviews, see Brauner-Osborne H et al. (2000) *J Med Chem.* 43:2609-45; Bordi F and Ugolini A. (1999) *Prog Neurobiol.* 59:55-79; Spooren W et al. (2003) *Behav Pharmacol.* 14:257-77).

The hypothesis of hypofunction of the glutamatergic system as reflected by NMDA receptor hypofunction as a putative cause of schizophrenia has received increasing support over the past few years (Goff DC and Coyle JT (2001) *Am J Psychiatry*, 158:1367-1377; Carlsson A et al. (2001) *Annu Rev Pharmacol Toxicol.*, 41:237-260 for a review). Evidence implicating dysfunction of glutamatergic neurotransmission is supported by the finding that antagonists of the NMDA subtype of glutamate receptor can reproduce the full range of symptoms as well as the physiologic manifestation of schizophrenia such as hypofrontality, impaired prepulse inhibition and enhanced subcortical dopamine release. In addition, clinical studies have suggested that mGluR5 allele frequency is associated with schizophrenia among certain cohorts (Devon RS et al. (2001) *Mol Psychiatry*, 6:311-4) and that an increase in mGluR5 message has been found in cortical pyramidal cells layers of schizophrenic brain (Ohnuma T et al. (1998) *Brain Res Mol Brain Res.* 56:207-17).

The involvement of mGluR5 in neurological and psychiatric disorders is supported by evidence showing that in vivo activation of group I mGluRs induces a potentiation of NMDA receptor function in a variety of brain regions mainly through the activation of mGluR5 receptors (Mannaioni G et al. (2001) *Neurosci.* 21:5925-34; Awad H et al. (2000) *J Neurosci* 20:7871-7879; Pisani A et al (2001) *Neuroscience* 106:579-87; Benquet P et al (2002) *J Neurosci.* 22:9679-86)

The role of glutamate in memory processes also has been firmly established during the past decade (Martin SJ et al. (2000) *Annu. Rev. Neurosci.* 23:649-711; Baudry M and Lynch G. (2001) *Neurobiol Learn Mem.*, 76:284-297). The use of mGluR5 null mutant mice have strongly supported a role of mGluR5 in learning and memory. These mice show a selective loss in two tasks of spatial learning and memory, and reduced CA1 LTP (Lu et al. (1997) *J. Neurosci.*, 17:5196-5205; Schulz B et al. (2001) *Neuropharmacology.* 41:1-7; Jia Z et al. (2001) *Physiol Behav.*, 73:793-802; Rodrigues et al. (2002) *J Neurosci.*, 22:5219-5229).

The finding that mGluR5 is responsible for the potentiation of NMDA receptors mediated currents raises the possibility that agonists of this receptor could be useful as cognitive-enhancing agents, but also, as novel antipsychotic agents that act by selectively enhancing NMDA receptor function

The activation of NMDARs could potentiate hypofunctional NMDARs in neuronal circuitry relevant to schizophrenia. Recent in vivo data strongly suggest that mGluR5 activation may be a novel and efficacious approach to treat to treat cognitive decline

and both positive and negative symptoms in schizophrenia (Kinney GG et al. (2002) 43:292).

mGluR5 receptor is therefore been considered as a potential drug target for treatment of psychiatric and neurological disorders including treatable diseases in this connection are Anxiety Disorders, Attentional disorders, Eating Disorders, Mood Disorders, Psychotic Disorders, Cognitive Disorders, Personality Disorders and Substance-related disorders

Most of the current modulators of mGluR5 function have been developed as structural analogues of glutamate, quisqualate or phenylglycine (Schoepp DD et al. (1999) *Neuropharmacology*, 38:1431-1476) and it has been very challenging to develop in vivo active and selective mGluR5 modulators acting at the glutamate binding site. A new avenue for developing selective modulators is to identify molecules that act through allosteric mechanisms, modulating the receptor by binding to site different from the highly conserved orthosteric binding site.

Positive allosteric modulators of mGluRs have emerged recently as novel pharmacological entities offering this attractive alternative. This type of molecule has been discovered for mGluR1, mGluR2, mGluR4, and mGluR5 (Knoflach F et al. (2001) *Proc Natl Acad Sci U S A*. 98:13402-13407; O'Brien JA et al. (2003) *Mol Pharmacol*. 64:731-40 ; Johnson K et al. (2002) *Neuropharmacology* 43:291; Johnson MP et al. (2003) *J Med Chem*. 46:3189-92; Marino MJ et al. (2003) *Proc Natl Acad Sci U S A*. Oct 30 [Epub ahead of print]; for a review see Mutel V (2002) *Expert Opin. Ther. Patents* 12:1-8). DFB and related molecules were described as mGluR5 positive allosteric modulator but with low in vitro potency (O'Brien JA et al. (2003) *Mol Pharmacol*. 64:731-40). Today no mGluR5 positive allosteric modulators showing in vivo activity are known and their in vitro activity is moderate..

Compounds of the present invention show surprisingly potent in vitro activity and demonstrate a biological activity in in vivo models.

The present invention relates to a method of treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR5 modulators.

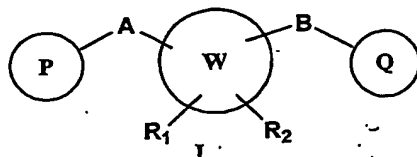
SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided new compounds substituted by a bridge A or B, with an unsaturated five or six aryl or heteroaryl ring containing atoms independently selected from carbon, nitrogen, sulfur and oxygen atoms. The invention also discloses pharmaceuticals acceptable form these new compounds.

Invention compounds are useful for treating CNS disorders which are affected by the neuromodulatory effect of mGluR5 enhancers such as cognitive decline and also to treat both positive and negative symptoms in schizophrenia.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, there are provided new compounds of the general formula I



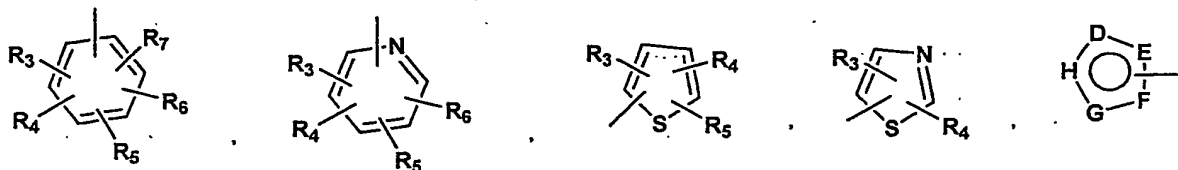
Or a pharmaceutically acceptable salt, hydrates or solvates of such compounds

Wherein

W represents a 5 to 7 atoms cycloalkyl or heterocycloalkyl ring.

R₁ and R₂ represent independently hydrogen, C₁-C₆-alkyl, C₁-C₆-alkenyl, C₁-C₆-alkynyl, arylalkyl, heteroarylalkyl, hydroxy, amino, aminoalkyl, hydroxyalkyl, C₁-C₆-alkoxy or R₁ and R₂ together can form a C₃-C₇-cycloalkyl ring, a carbonyl bond C=O or a carbon double bond.

P and Q are each independently selected and denote an aryl or heteroaryl group of formula



R₃, R₄, R₅, R₆, and R₇ independently are hydrogen, halogen, -CN, nitro, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₃-C₇-cycloalkylalkyl, C₁-C₆-alkenyl, C₁-C₆-alkynyl, halo-C₁-C₆-alkyl, -heteroaryl, heteroarylalkyl, arylalkyl, aryl, -OR₈, -NR₈R₉, -C(=NR₁₀)NR₈R₉, N(=NR₁₀)NR₈R₉, -NR₈COR₉, NR₈CO₂R₉, NR₈SO₂R₉, -NR₁₀CO NR₈R₉, -SR₈, -S(=O)R₈, -S(=O)₂R₈, -S(=O)₂NR₈R₉, -C(=O)R₈, -C(=O)₂R₈, -C(=O)NR₈R₉, -C(=NR₈)R₉, or C(=NOR₈)R₉ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic aryl or heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, -CN, C₁-C₆-alkyl, -O(C₀-C₆-alkyl), -O(C₃-C₇-cycloalkylalkyl), -O(aryl), -O(heteroaryl), -O(C₁-C₃-alkylaryl), -O(C₁-C₃-alkylheteroaryl), -N(C₀-C₆-alkyl)(C₀-C₃-alkylaryl) or -N(C₀-C₆-alkyl)(C₀-C₃-alkylheteroaryl) groups;

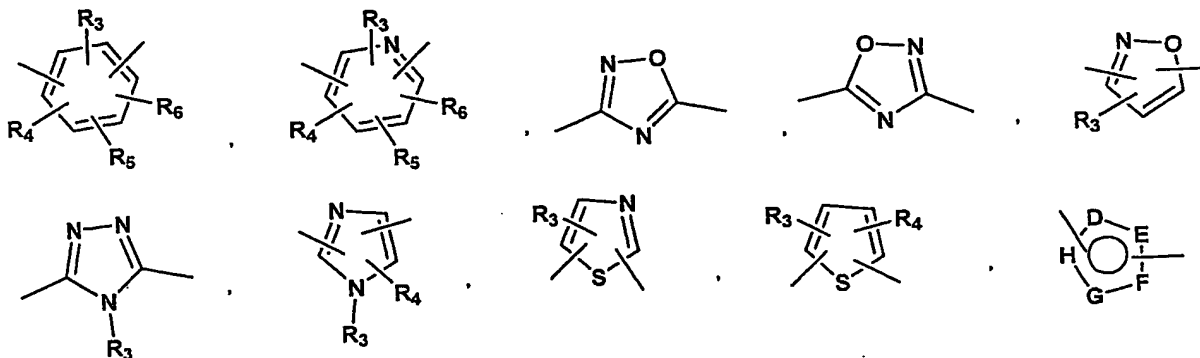
R₈, R₉, R₁₀ each independently is hydrogen, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₃-C₇-cycloalkylalkyl, -C₆-alkenyl, C₁-C₆-alkynyl, halo-C₁-C₆-alkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, C₁-C₆-alkyl, -O(C₀-C₆-alkyl), -O(C₃-C₇-cycloalkylalkyl), -O(aryl), -

O(heteroaryl), $-N(C_0-C_6\text{-alkyl})(C_0-C_6\text{-alkyl})$, $-N(C_0-C_6\text{-alkyl})(C_3-C_7\text{-cycloalkyl})$ or $-N(C_0-C_6\text{-alkyl})(\text{aryl})$ substituents;

D, E, F, G and H represent independently $-C(R_3)=$, $-C(R_3)=C(R_4)-$, $-C(=O)-$, $-C(=S)-$, $-O-$, $-N=$, $-N(R_3)-$ or $-S-$.

A

is azo $-N=N-$, ethyl, ethenyl, ethynyl, $-NR_8C(=O)-$, $NR_8S(=O)_2-$, $-C(=O)NR_8-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-S(=O)_2NR_8-$, $-C(=O)-O-$, $-O-C(=O)-$, $-C(=NR_8)NR_9-$, $C(=NOR_8)NR_9-$, $-NR_8C(=NOR_9)-$, $=N-O-$, $-O-N=CH-$ or a group aryl or heteroaryl of formula



R_3 , R_4 , R_5 and R_6 independently are as defined above.
D, E, F, G represents oxygen, nitrogen, sulphur or a double bond.

B

represents a single bond, $-C(=O)-C_0-C_2\text{-alkyl}-$, $C(=O)-O-$, $-C(=O)NR_8-C_0-C_2\text{-alkyl}-$, $-C(=NR_8)NR_9-S(=O)-C_0-C_2\text{-alkyl}-$, $-S(=O)_2-C_0-C_2\text{-alkyl}-$, $-S(=O)_2NR_8-C_0-C_2\text{-alkyl}-$, $C(=NR_8)-C_0-C_2\text{-alkyl}-$, $-C(=NOR_8)-C_0-C_2\text{-alkyl}-$ or $-C(=NOR_8)NR_9-C_0-C_2\text{-alkyl}-$;
 R_8 and R_9 , independently are as defined above.

Any N may be an N-oxyde.

The present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well.

In the above definition, the term " $C_1-C_6\text{-alkyl}$ " includes group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl or the like.

" $C_1-C_6\text{-alkenyl}$ " includes group such as ethenyl, 1-propenyl, allyl, isopropenyl, 1-butenyl, 3-butenyl, 4-pentenyl and the like.

" $C_1-C_6\text{-alkynyl}$ " includes group such as ethynyl, propynyl, butynyl, pentynyl and the like.

"Halogen" includes atoms such as fluorine, bromine, chlorine and iodine.

"Aryl" includes C₆-C₁₀ aryl group such as phenyl, 1-naphtyl, 2-naphtyl and the like.

"Arylalkyl" includes C₆-C₁₀ aryl-C₁-C₃-alkyl group such as benzyl group, 1-phenylethyl group, 2-phenylethyl group, 1-phenylpropyl group, 2-phenylpropyl group, 3-phenylpropyl group, 1-naphtylmethyl group, 2-naphtylmethyl group or the like.

"Heteroaryl" includes 5-10 membered heterocyclic group containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur to form a ring such as furyl (furan ring), benzofuranyl (benzofuran), thienyl (thiophene), benzothiophenyl (benzothiophene), pyrrolyl (pyrrole ring), imidazolyl (imidazole ring), pyrazolyl (pyrazole ring), thiazolyl (thiazole ring), isothiazolyl (isothiazole ring), triazolyl (triazole ring), tetrazolyl (tetrazole ring), pyridil (pyridine ring), pyrazynyl (pyrazine ring), pyrimidinyl (pyrimidine ring), pyridazinyl (pyridazine ring), indolyl (indole ring), isoindolyl (isoindole ring), benzoimidazolyl (benzimidazole ring), purinyl group (purine ring), quinolyl (quinoline ring), phtalazinyl (phtalazine ring), naphtyridinyl (naphtyridine ring), quinoxalinyl (quinoxaline ring), cinnolyl (cinnoline ring), pteridinyl (pteridine ring), oxazolyl (oxazole ring), isoxazolyl (isoxazole ring), benzoxazolyl (benzoxazole ring), benzothiazolyl (benzothiazole ring), furazanyl (furazan ring) and the like.

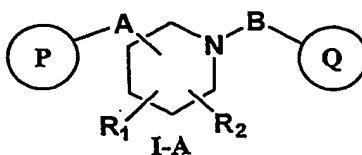
"Heteroarylalkyl" includes heteroaryl-C₁-C₃-alkyl group, wherein examples of heteroaryl are the same as those illustrated in the above definition, such as 2-furylmethyl group, 3-furylmethyl group, 2-thienylmethyl group, 3-thienylmethyl group, 1-imidazolylmethyl group, 2-imidazolylmethyl group, 2-thiazolylmethyl group, 2-pyridylmethyl group, 3-pyridylmethyl group, 1-quinolylmethyl group or the like.

"Solvate" refers to a complex of variable stoichiometry formed by a solute (e.g. a compound of formula I) and a solvent. The solvent is a pharmaceutically acceptable solvent as water preferably; such solvent may not interfere with the biological activity of the solute.

"Optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s), which occur, and events that do not occur.

The term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

Preferred compounds of the present invention are compounds of formula I-A depicted below

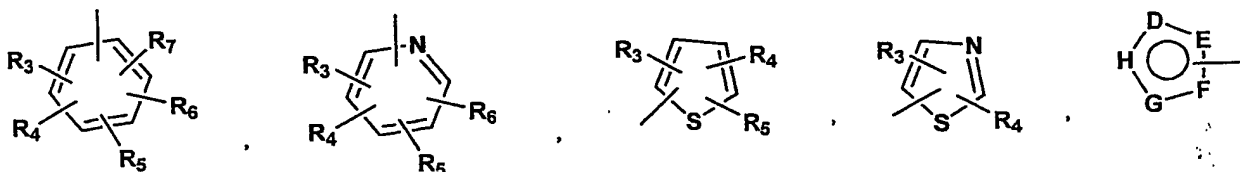


Or a pharmaceutically acceptable salt, hydrates or solvates of such compounds

Wherein

R_1 and R_2 represent independently hydrogen, C_1 - C_6 -alkyl, C_1 - C_6 -alkenyl, C_1 - C_6 -alkynyl, arylalkyl, heteroarylalkyl, hydroxy, amino, aminoalkyl, hydroxyalkyl, C_1 - C_6 -alkoxy or R_1 and R_2 together can form a C_3 - C_7 -cycloalkyl ring, a carbonyl bond $C=O$ or a carbon double bond.

P and Q are each independently selected and denote an aryl or heteroaryl group of formula



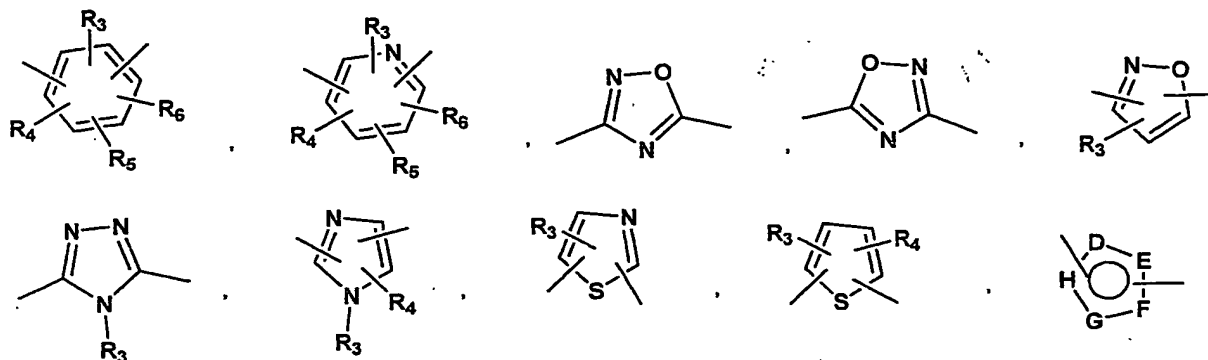
R_3 , R_4 , R_5 , R_6 , and R_7 independently are hydrogen, halogen, $-CN$, nitro, C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl, C_3 - C_7 -cycloalkylalkyl, C_1 - C_6 -alkenyl, C_1 - C_6 -alkynyl, halo- C_1 - C_6 -alkyl, -heteroaryl, heteroarylalkyl, arylalkyl, aryl, - OR_8 , $-NR_8R_9$, $-C(=NR_{10})NR_8R_9$, $N(=NR_{10})NR_8R_9$, $-NR_8COR_9$, $NR_8CO_2R_9$, $NR_8SO_2R_9$, $-NR_{10}CO NR_8R_9$, $-SR_8$, $-S(=O)R_8$, $-S(=O)_2R_8$, $-S(=O)_2NR_8R_9$, $-C(=O)R_8$, $-C(=O)_2R_8$, $-C(=O)NR_8R_9$, $-C(=NR_8)R_9$, or $C(=NOR_8)R_9$ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic aryl or heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, $-CN$, C_1 - C_6 -alkyl, $-O(C_0$ - C_6 -alkyl), $-O(C_3$ - C_7 -cycloalkylalkyl), $-O(aryl)$, $-O(heteroaryl)$, $-O(C_1$ - C_3 -alkylaryl), $-O(C_1$ - C_3 -alkylheteroaryl), $-N(C_0$ - C_6 -alkyl)(C_0 - C_3 -alkylaryl) or $-N(C_0$ - C_6 -alkyl)(C_0 - C_3 -alkylheteroaryl) groups;

R_8 , R_9 , R_{10} each independently is hydrogen, C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl, C_3 - C_7 -cycloalkylalkyl, $-C_6$ -alkenyl, C_1 - C_6 -alkynyl, halo- C_1 - C_6 -alkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, $-CN$, C_1 - C_6 -alkyl, $-O(C_0$ - C_6 -alkyl), $-O(C_3$ - C_7 -cycloalkylalkyl), $-O(aryl)$, $-O(heteroaryl)$, $-N(C_0$ - C_6 -alkyl)(C_0 - C_6 -alkyl), $-N(C_0$ - C_6 -alkyl)(C_3 - C_7 -cycloalkyl) or $-N(C_0$ - C_6 -alkyl)(aryl) substituents;

D , E , F , G and H represent independently $-C(R_3)=$, $-C(R_3)=C(R_4)-$, $-C(=O)-$, $-C(=S)-$, $-O-$, $-N=$, $-N(R_3)-$ or $-S-$.

A

is azo $-N=N-$, ethyl, ethenyl, ethynyl, $-NR_8C(=O)-$, $NR_8S(=O)_2-$, $-C(=O)NR_8-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-S(=O)_2NR_8-$, $-C(=O)-O-$, $-O-C(=O)-$, $-C(=NR_8)NR_9-$, $C(=NOR_8)NR_9-$, $-NR_8C(=NOR_9)-$, $=N-O-$, $-O-N=CH-$ or a group aryl or heteroaryl of formula



R_3 , R_4 , R_5 and R_6 independently are as defined above.

D , E , F , G and H independently are as defined above.

B

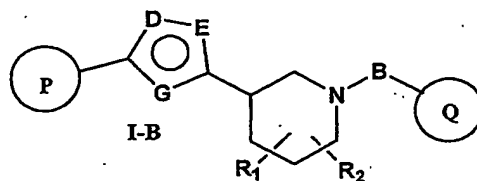
represents a single bond, $-C(=O)-C_0-C_2$ -alkyl-, $C(=O)-O-$, $-C(=O)NR_8-C_0-C_2$ -alkyl-, $-C(=NR_8)NR_9-S(=O)-C_0-C_2$ -alkyl-, $-S(=O)_2-C_0-C_2$ -alkyl-, $-S(=O)_2NR_8-C_0-C_2$ -alkyl-, $C(=NR_8)-C_0-C_2$ -alkyl-, $-C(=NOR_8)-C_0-C_2$ -alkyl- or $-C(=NOR_8)NR_9-C_0-C_2$ -alkyl-;
 R_8 and R_9 , independently are as defined above.

Any N may be an N-oxyde.

The present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well.

More preferred compounds of the present invention are compounds of formula

I-B



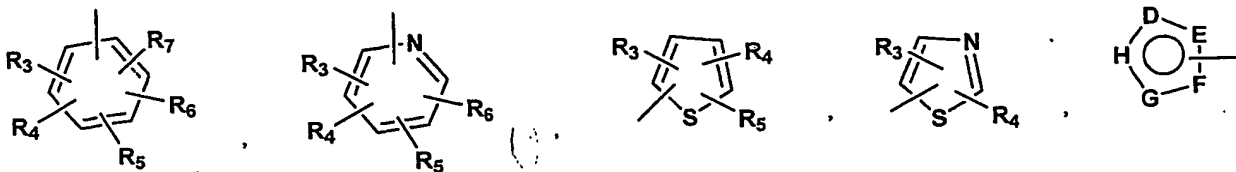
Or a pharmaceutically acceptable salt, hydrates or solvates of such compounds

Wherein

R_1 and R_2 represent independently hydrogen, C_1-C_6 -alkyl, C_1-C_6 -alkenyl, C_1-C_6 -alkynyl, arylalkyl, heteroarylalkyl, hydroxy, amino, aminoalkyl,

hydroxyalkyl, C₁-C₆alkoxy or R₁ and R₂ together can form a C₃-C₇-cycloalkyl ring, a carbonyl bond C=O or a carbon double bond.

P and Q are each independently selected and denote an aryl or heteroaryl group of formula



R₃, R₄, R₅, R₆, and R₇ independently are hydrogen, halogen, -CN, nitro, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₃-C₇-cycloalkylalkyl, C₁-C₆-alkenyl, C₁-C₆-alkynyl, halo-C₁-C₆-alkyl, -heteroaryl, heteroarylalkyl, arylalkyl, aryl, -OR₈, -NR₈R₉, -C(=NR₁₀)NR₈R₉, N(=NR₁₀)NR₈R₉, -NR₈COR₉, NR₈CO₂R₉, NR₈SO₂R₉, -NR₁₀CO NR₈R₉, -SR₈, -S(=O)R₈, -S(=O)₂R₈, -S(=O)₂NR₈R₉, -C(=O)R₈, -C(=O)₂R₈, -C(=O)NR₈R₉, -C(=NR₈)R₉, or C(=NOR₈)R₉ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic aryl or heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, -CN, C₁-C₆-alkyl, -O(C₀-C₆-alkyl), -O(C₃-C₇-cycloalkylalkyl), -O(aryl), -O(heteroaryl), -O(C₁-C₃-alkylaryl), -O(C₁-C₃-alkylheteroaryl), -N(C₀-C₆-alkyl)(C₀-C₃-alkylaryl) or -N(C₀-C₆-alkyl)(C₀-C₃-alkylheteroaryl) groups;

R₈, R₉, R₁₀ each independently is hydrogen, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₃-C₇-cycloalkylalkyl, -C₆-alkenyl, C₁-C₆-alkynyl, halo-C₁-C₆-alkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, C₁-C₆-alkyl, -O(C₀-C₆-alkyl), -O(C₃-C₇-cycloalkylalkyl), -O(aryl), -O(heteroaryl), -N(C₀-C₆-alkyl)(C₀-C₆-alkyl), -N(C₀-C₆-alkyl)(C₃-C₇-cycloalkyl) or -N(C₀-C₆-alkyl)(aryl) substituents;

D, E, F, G and H represent independently -C(R₃)=, -C(R₃)=C(R₄)-, -C(=O)-, -C(=S)-, -O-, -N=, -N(R₃)- or -S-.

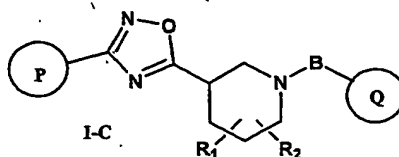
D, E, F, G and H independently are as defined above..

B represents a single bond, -C(=O)-C₀-C₂-alkyl-, C(=O)-O-, -C(=O)NR₈-C₀-C₂-alkyl-, -C(=NR₈)NR₉-S(=O)-C₀-C₂-alkyl-, -S(=O)₂-C₀-C₂-alkyl-, -S(=O)₂NR₈-C₀-C₂-alkyl-, C(=NR₈)-C₀-C₂-alkyl-, -C(=NOR₈)-C₀-C₂-alkyl- or -C(=NOR₈)NR₉-C₀-C₂-alkyl-; R₈ and R₉ independently are as defined above.

Any N may be an N-oxide.

The present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well.

Particularly preferred compounds of the present invention are compounds of formula I-C

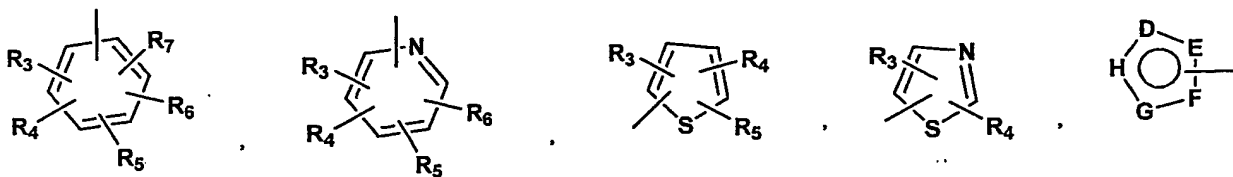


Or a pharmaceutically acceptable salt, hydrates or solvates of such compounds

Wherein

R_1 and R_2 represent independently hydrogen, C_1 - C_6 -alkyl, C_1 - C_6 -alkenyl, C_1 - C_6 -alkynyl, arylalkyl, heteroarylalkyl, hydroxy, hydroxyalkyl, C_1 - C_6 -alkoxy or R_1 and R_2 together can form a carbonyl bond $C=O$ or a carbon double bond.

P and Q are each independently selected and denote an aryl or heteroaryl group of formula



R_3 , R_4 , R_5 , R_6 , and R_7 independently are hydrogen, halogen, -CN, nitro, C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl, C_3 - C_7 -cycloalkylalkyl, C_1 - C_6 -alkenyl, C_1 - C_6 -alkynyl, halo- C_1 - C_6 -alkyl, -heteroaryl, heteroarylalkyl, arylalkyl, aryl, -OR₈, -NR₈R₉, -C(=NR₁₀)NR₈R₉, N(=NR₁₀)NR₈R₉, -NR₈COR₉, NR₈CO₂R₉, NR₈SO₂R₉, -NR₁₀CO NR₈R₉, -SR₈, -S(=O)R₈, -S(=O)₂R₈, -S(=O)₂NR₈R₉, -C(=O)R₈, -C(=O)₂R₈, -C(=O)NR₈R₉, -C(=NR₈)R₉, or C(=NOR₈)R₉ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic aryl or heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, -CN, C_1 - C_6 -alkyl, -O(C_0 - C_6 -alkyl), -O(C_3 - C_7 -cycloalkylalkyl), -O(aryl), -O(heteroaryl), -O(C_1 - C_3 -alkylaryl), -O(C_1 - C_3 -alkylheteroaryl), -N(C_0 - C_6 -alkyl)(C_0 - C_3 -alkylaryl) or -N(C_0 - C_6 -alkyl)(C_0 - C_3 -alkylheteroaryl) groups;

R_8 , R_9 , R_{10} each independently is hydrogen, C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl, C_3 - C_7 -cycloalkylalkyl, - C_6 -alkenyl, C_1 - C_6 -alkynyl, halo- C_1 - C_6 -alkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, C_1 - C_6 -alkyl, -O(C_0 - C_6 -alkyl), -O(C_3 - C_7 -cycloalkylalkyl), -O(aryl), -O(heteroaryl), -N(C_0 - C_6 -alkyl)(C_0 - C_6 -alkyl), -N(C_0 - C_6 -alkyl)(C_3 - C_7 -cycloalkyl) or -N(C_0 - C_6 -alkyl)(aryl) substituents;

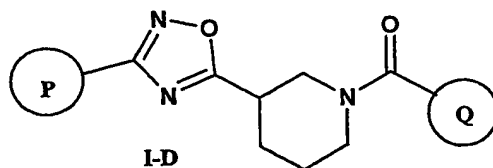
D, E, F, G and H represent independently $-C(R_3)=$, $-C(R_3)=C(R_4)-$, $-C(=O)-$, $-C(=S)-$, $-O-$, $-N=$, $-N(R_3)-$ or $-S-$.

B represents a single bond, $-C(=O)-C_0-C_2$ -alkyl-, $C(=O)-O-$, $-C(=O)NR_8-C_0-C_2$ -alkyl-, $-C(=NR_8)NR_9-S(=O)-C_0-C_2$ -alkyl-, $-S(=O)_2-C_0-C_2$ -alkyl-, $-S(=O)_2NR_8-C_0-C_2$ -alkyl-, $C(=NR_8)-C_0-C_2$ -alkyl-, $-C(=NOR_8)-C_0-C_2$ -alkyl- or $-C(=NOR_8)NR_9-C_0-C_2$ -alkyl-; R_8 and R_9 , independently are as defined above.

Any N may be an N-oxyde.

The present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well.

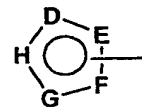
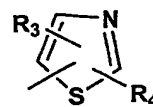
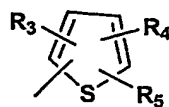
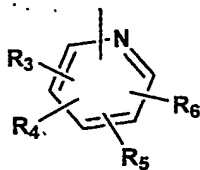
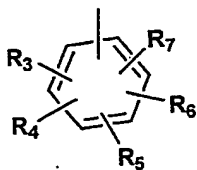
Further preferred compounds of the present invention are compounds of formula I-D



Or a pharmaceutically acceptable salt, hydrates or solvates of such compounds

Wherein

P and Q are each independently selected and denote an aryl or heteroaryl group of formula



R_3, R_4, R_5, R_6 , and R_7 independently are hydrogen, halogen, $-CN$, nitro, C_1-C_6 -alkyl, C_3-C_6 -cycloalkyl, C_3-C_7 -cycloalkylalkyl, C_1-C_6 -alkenyl, C_1-C_6 -alkynyl, halo- C_1-C_6 -alkyl, -heteroaryl, heteroarylalkyl, arylalkyl, aryl, $-OR_8$, $-NR_8R_9$, $-C(=NR_{10})NR_8R_9$, $N(=NR_{10})NR_8R_9$, $-NR_8COR_9$, $NR_8CO_2R_9$, $NR_8SO_2R_9$, $-NR_{10}CO NR_8R_9$, $-SR_8$, $-S(=O)R_8$, $-S(=O)_2R_8$, $-S(=O)_2NR_8R_9$, $-C(=O)R_8$, $-C(=O)_2R_8$, $-C(=O)NR_8R_9$, $-C(=NR_8)R_9$, or $C(=NOR_8)R_9$ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic aryl or heteroaryl ring; wherein each ring is optionally further substituted with

1-5 independent halogen, -CN, C₁-C₆-alkyl, -O(C₀-C₆-alkyl), -O(C₃-C₇-cycloalkylalkyl), -O(aryl), -O(heteroaryl), -O(C₁-C₃-alkylaryl), -O(C₁-C₃-alkylheteroaryl), -N(C₀-C₆-alkyl)(C₀-C₃-alkylaryl) or -N(C₀-C₆-alkyl)(C₀-C₃-alkylheteroaryl) groups;

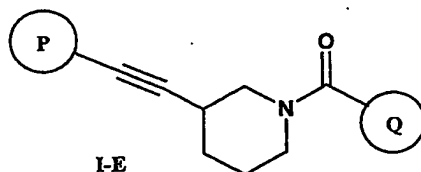
R₈, R₉, R₁₀ each independently is hydrogen, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₃-C₇-cycloalkylalkyl, -C₆-alkenyl, C₁-C₆-alkynyl, halo-C₁-C₆-alkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, C₁-C₆-alkyl, -O(C₀-C₆-alkyl), -O(C₃-C₇-cycloalkylalkyl), -O(aryl), -O(heteroaryl), -N(C₀-C₆-alkyl)(C₀-C₆-alkyl), -N(C₀-C₆-alkyl)(C₃-C₇-cycloalkyl) or -N(C₀-C₆-alkyl)(aryl) substituents;

D, E, F, G and H represent independently -C(R₃)=, -C(R₃)=C(R₄)-, -C(=O)-, -C(=S)-, -O-, -N=, -N(R₃)- or -S-.

Any N may be an N-oxyde.

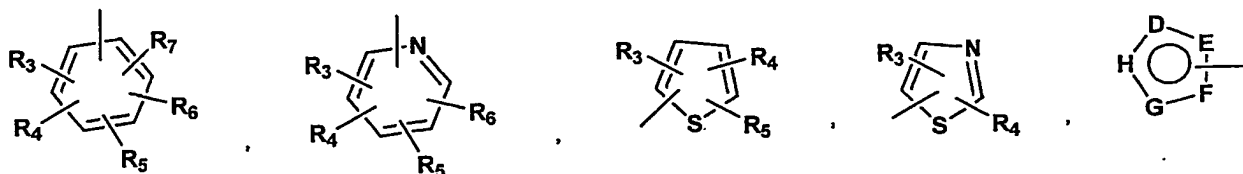
The present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well.

In another aspect, the compound of this invention is represented by formula (I-E) or a pharmaceutically acceptable salt thereof



Wherein

P and Q are each independently selected and denote an aryl or heteroaryl group of formula



R₃, R₄, R₅, R₆, and R₇ independently are hydrogen, halogen, -CN, nitro, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₃-C₇-cycloalkylalkyl, C₁-C₆-alkenyl, C₁-C₆-alkynyl, halo-C₁-C₆-alkyl, -heteroaryl, heteroarylalkyl, arylalkyl, aryl, -OR₈, -NR₈R₉, -C(=NR₁₀)NR₈R₉, N(=NR₁₀)NR₈R₉, -NR₈COR₉, NR₈CO₂R₉, NR₈SO₂R₉, -NR₁₀CO NR₈R₉, -SR₈, -S(=O)R₈, -S(=O)₂R₈, -S(=O)₂NR₈R₉, -C(=O)R₈, -C(=O)₂R₈, -C(=O)NR₈R₉, -C(=NR₈)R₉, or C(=NOR₈)R₉ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic aryl or

heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, -CN, C₁-C₆-alkyl, -O(C₀-C₆-alkyl), -O(C₃-C₇-cycloalkylalkyl), -O(aryl), -O(heteroaryl), -O(C₁-C₃-alkylaryl), -O(C₁-C₃-alkylheteroaryl), -N(C₀-C₆-alkyl)(C₀-C₃-alkylaryl) or -N(C₀-C₆-alkyl)(C₀-C₃-alkylheteroaryl) groups;

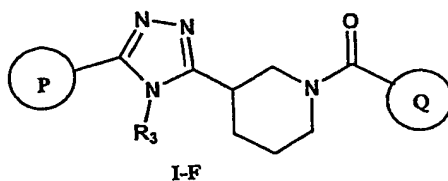
R₈, R₉, R₁₀ each independently is hydrogen, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₃-C₇-cycloalkylalkyl, -C₆-alkenyl, C₁-C₆-alkynyl, halo-C₁-C₆-alkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, C₁-C₆-alkyl, -O(C₀-C₆-alkyl), -O(C₃-C₇-cycloalkylalkyl), -O(aryl), -O(heteroaryl), -N(C₀-C₆-alkyl)(C₀-C₆-alkyl), -N(C₀-C₆-alkyl)(C₃-C₇-cycloalkyl) or -N(C₀-C₆-alkyl)(aryl) substituents;

D, E, F, G and H represent independently -C(R₃)=, -C(R₃)=C(R₄)-, -C(=O)-, -C(=S)-, -O-, -N=, -N(R₃)- or -S-.

Any N may be an N-oxyde.

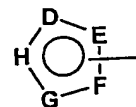
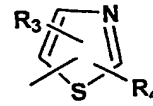
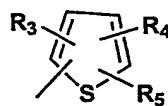
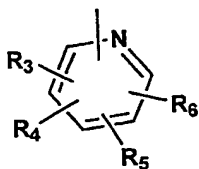
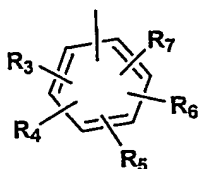
The present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well.

In further aspect, the compound of this invention is represented by formula (I-F) or a pharmaceutically acceptable salt thereof



Wherein

P and Q are each independently selected and denote an aryl or heteroaryl group of formula



R₃, R₄, R₅, R₆, and R₇ independently are hydrogen, halogen, -CN, nitro, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₃-C₇-cycloalkylalkyl, C₁-C₆-alkenyl, C₁-C₆-alkynyl, halo-C₁-C₆-alkyl, -heteroaryl, heteroarylalkyl, arylalkyl, aryl, -OR₈, -NR₈R₉, -C(=NR₁₀)NR₈R₉, N(=NR₁₀)NR₈R₉, -NR₈COR₉, NR₈CO₂R₉, NR₈SO₂R₉, -NR₁₀CO NR₈R₉, -SR₈, -S(=O)R₈, -S(=O)₂R₈, -S(=O)₂NR₈R₉, -C(=O)R₈, -C(=O)₂R₈, -C(=O)NR₈R₉, -C(=NR₈)R₉, or C(=NOR₈)R₉ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic aryl or

heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, -CN, C₁-C₆-alkyl, -O(C₀-C₆-alkyl), -O(C₃-C₇-cycloalkylalkyl), -O(aryl), -O(heteroaryl), -O(C₁-C₃-alkylaryl), -O(C₁-C₃-alkylheteroaryl), -N(C₀-C₆-alkyl)(C₀-C₃-alkylaryl) or -N(C₀-C₆-alkyl)(C₀-C₃-alkylheteroaryl) groups;

R₈, R₉, R₁₀ each independently is hydrogen, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₃-C₇-cycloalkylalkyl, -C₆-alkenyl, C₁-C₆-alkynyl, halo-C₁-C₆-alkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, C₁-C₆-alkyl, -O(C₀-C₆-alkyl), -O(C₃-C₇-cycloalkylalkyl), -O(aryl), -O(heteroaryl), -N(C₀-C₆-alkyl)(C₀-C₆-alkyl), -N(C₀-C₆-alkyl)(C₃-C₇-cycloalkyl) or -N(C₀-C₆-alkyl)(aryl) substituents;

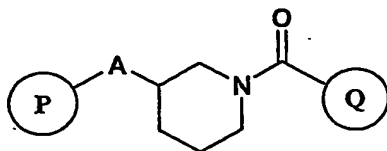
D, E, F, G and H represent independently -C(R₃)=, -C(R₃)=C(R₄)-, -C(=O)-, -C(=S)-, -O-, -N=, -N(R₃)- or -S-.

Any N may be an N-oxyde.

The present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well.

Examples of the compounds of the present invention are set forth in Table I and II:

TABLE I:



P	A	Q

TABLE I (continued):

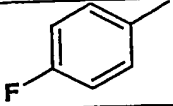
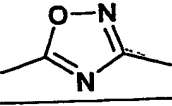
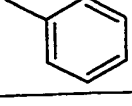
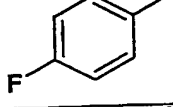
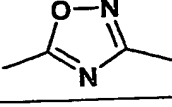
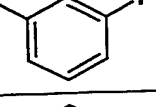
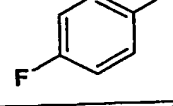
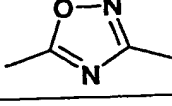
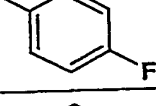
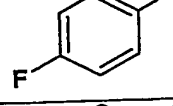
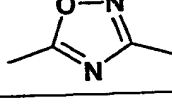
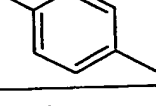
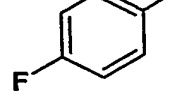
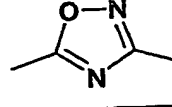
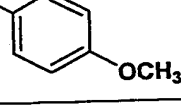
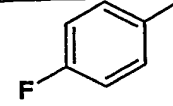
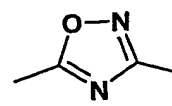
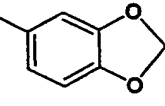
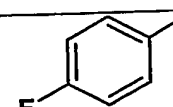
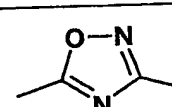
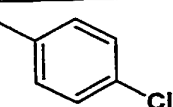
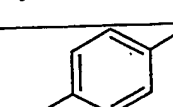
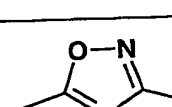
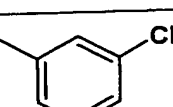
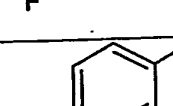
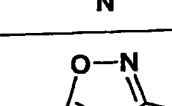
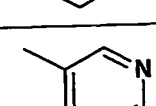
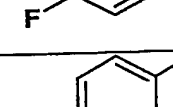
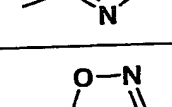
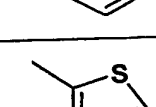
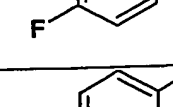
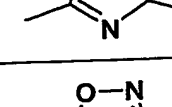
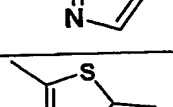
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

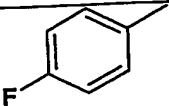
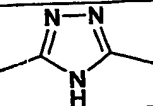
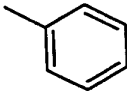
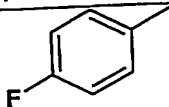
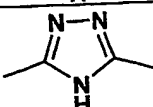
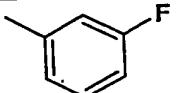
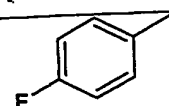
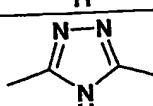
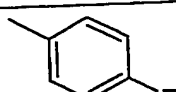
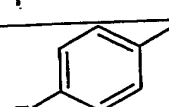
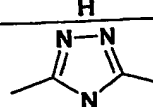
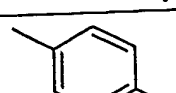
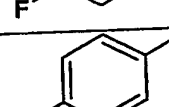
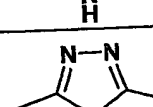
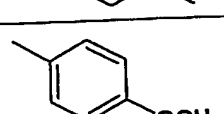
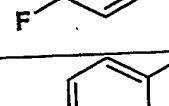
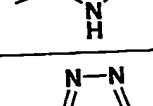
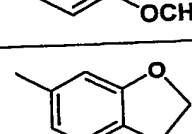
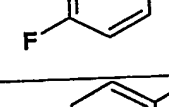
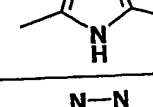
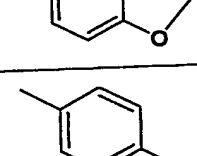
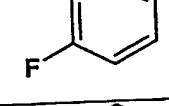
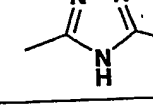
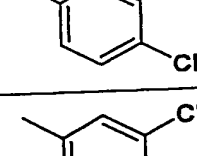
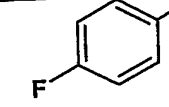
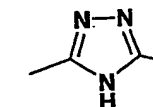
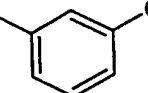
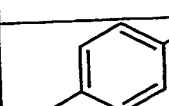
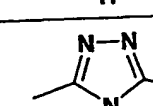
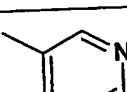
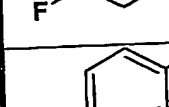
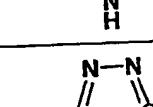
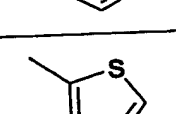
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

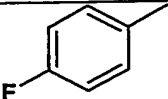
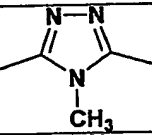
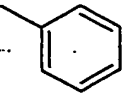
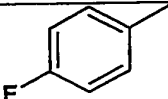
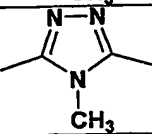
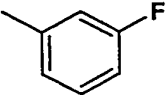
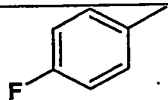
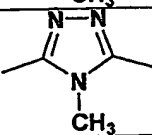
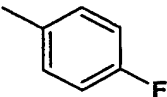
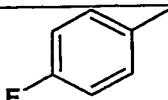
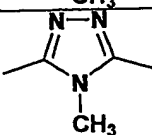
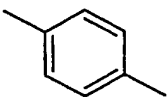
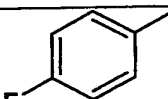
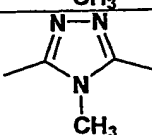
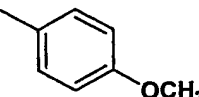
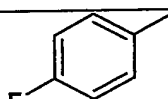
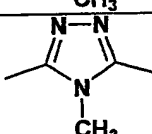
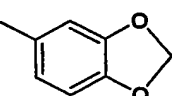
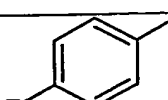
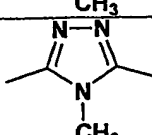
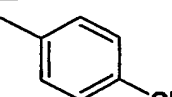
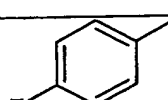
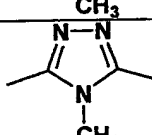
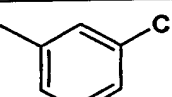
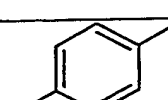
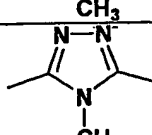
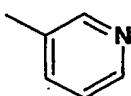
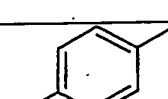
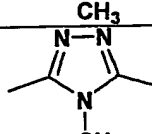
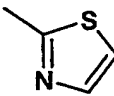
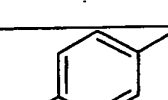
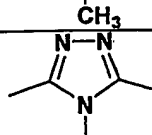
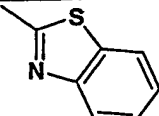
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

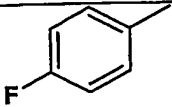
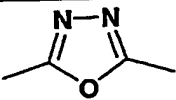
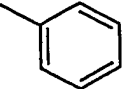
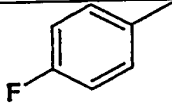
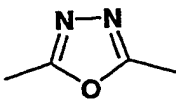
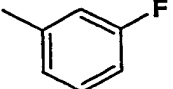
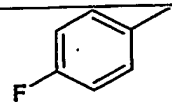
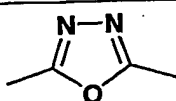
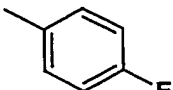
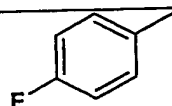
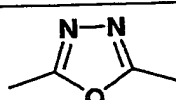
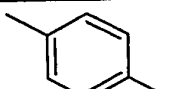
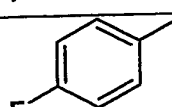
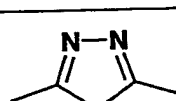
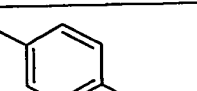
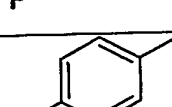
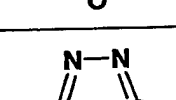
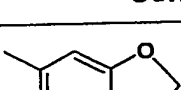
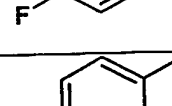
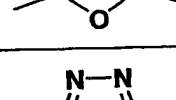
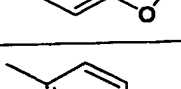
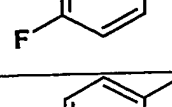
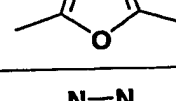
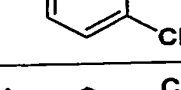
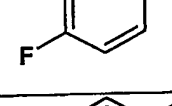
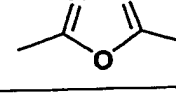
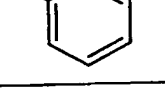
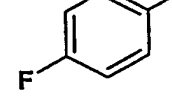
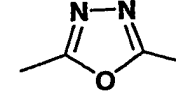
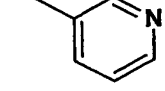
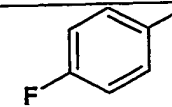
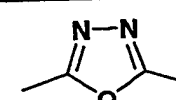
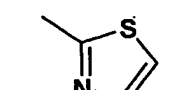
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

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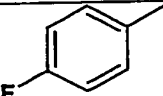
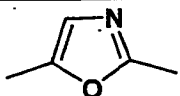
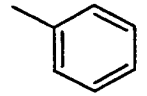
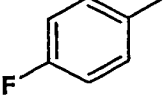
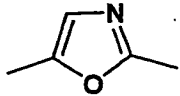
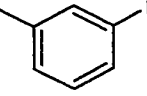
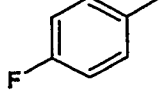
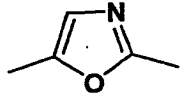
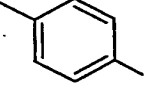
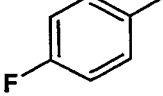
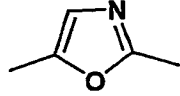
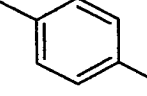
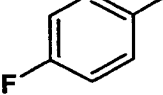
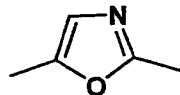
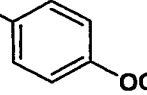
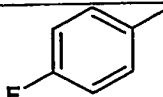
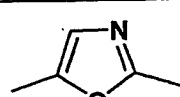
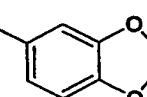
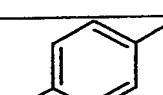
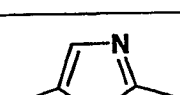
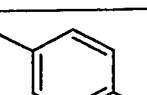

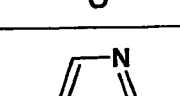
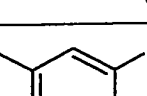
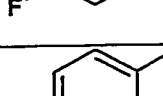
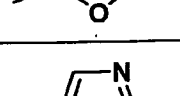
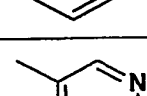
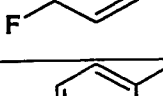
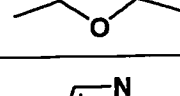
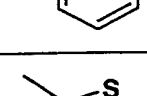
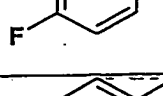
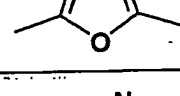
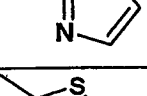
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

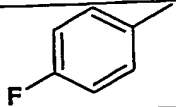
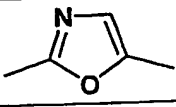
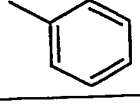
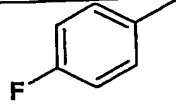
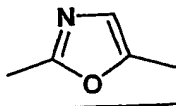
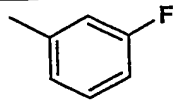
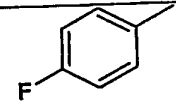
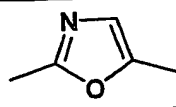
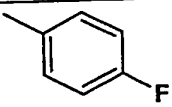
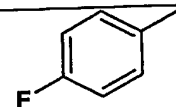
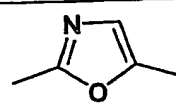
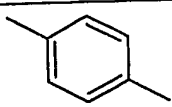
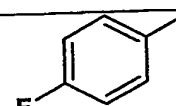
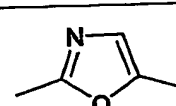
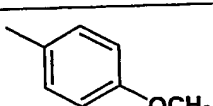
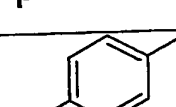
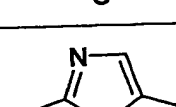
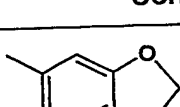
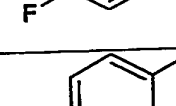
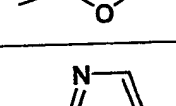
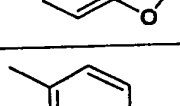
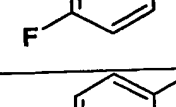
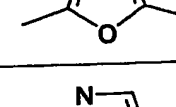
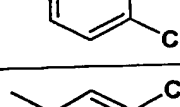
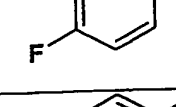
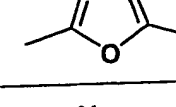
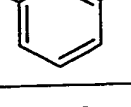
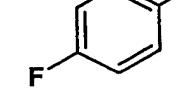
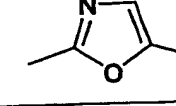
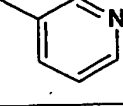
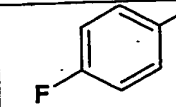
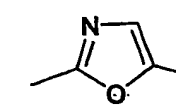
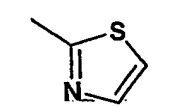
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

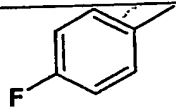
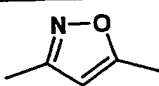
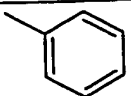
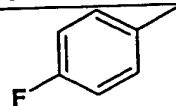
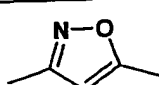
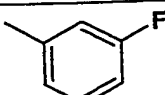
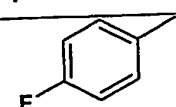
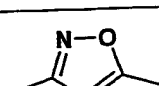
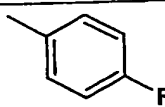
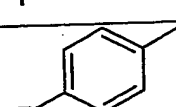
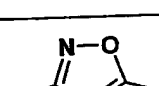
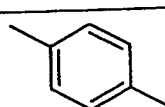
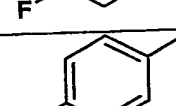
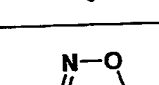
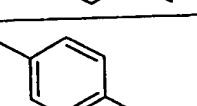
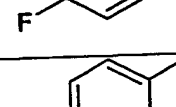
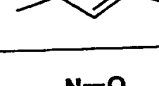
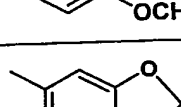
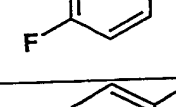
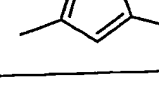
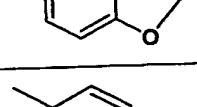
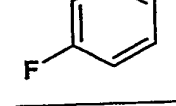
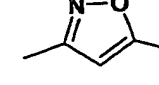
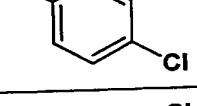
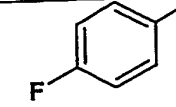
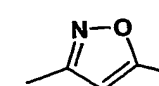
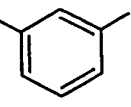
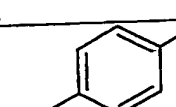
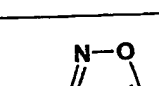
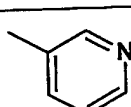
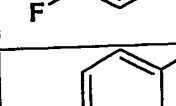
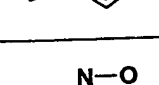
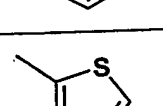
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

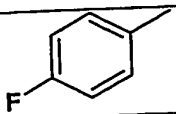
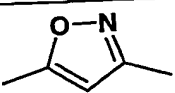
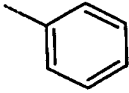
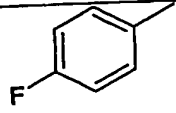
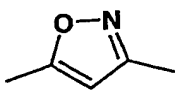
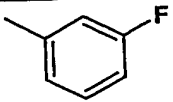
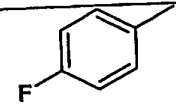
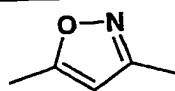
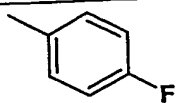
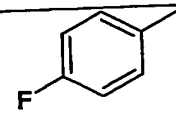
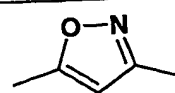
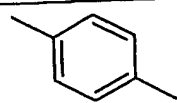
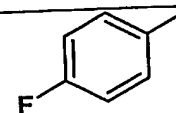
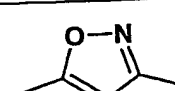
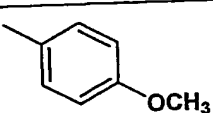
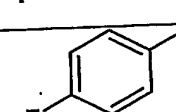
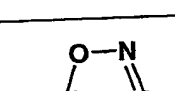
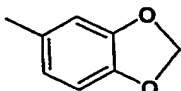

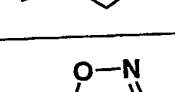
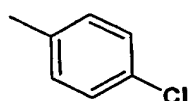
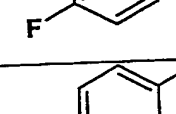
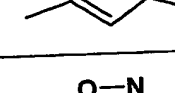
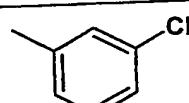
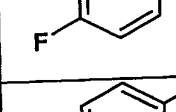
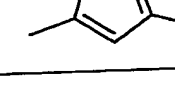
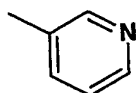
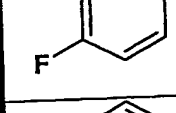
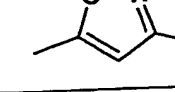
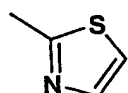
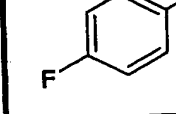
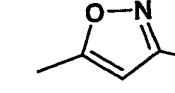
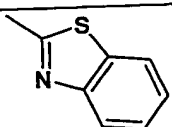
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

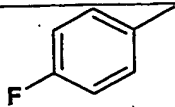
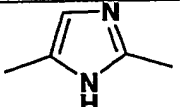
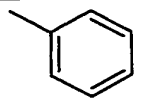
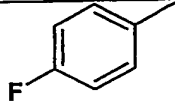
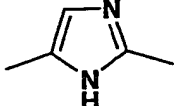
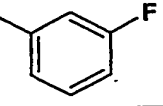
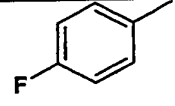
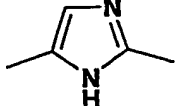
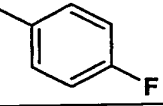
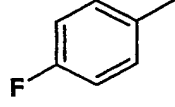
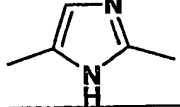
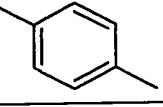
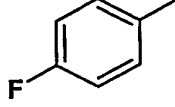
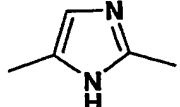
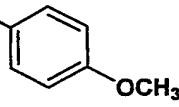
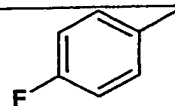
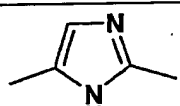
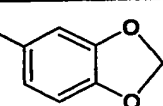
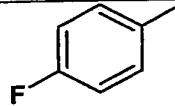
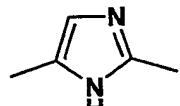
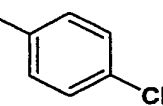
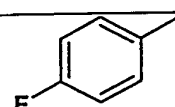
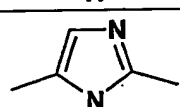
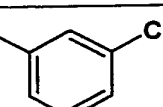
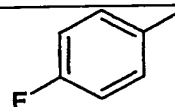
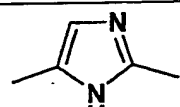
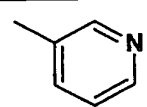
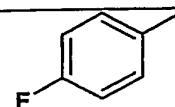
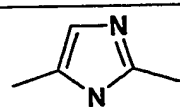
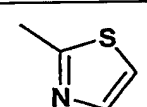
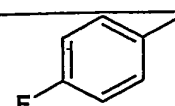
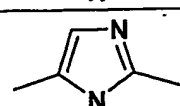
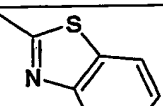
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

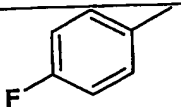
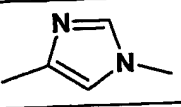
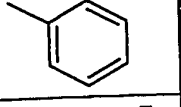
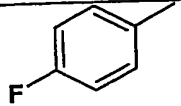
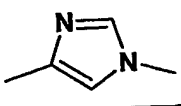
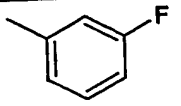
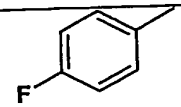
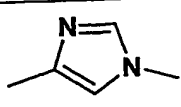
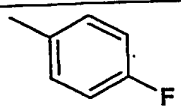
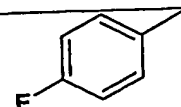
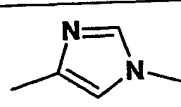
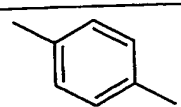
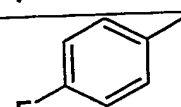
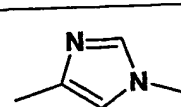
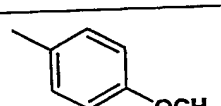
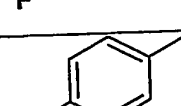
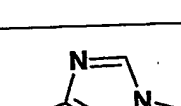
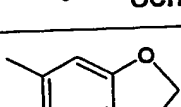
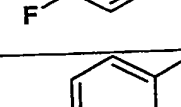
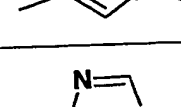
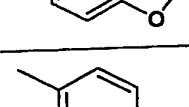
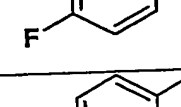
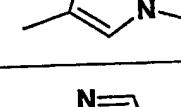
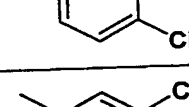
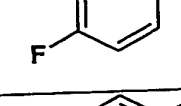
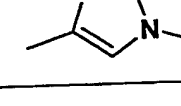
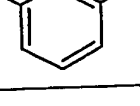
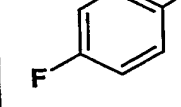
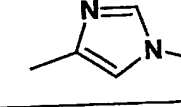
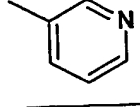
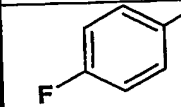
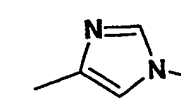
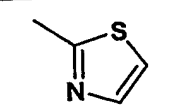
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

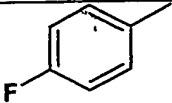
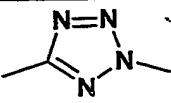
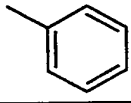
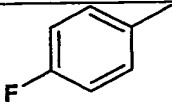
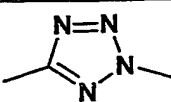
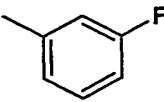
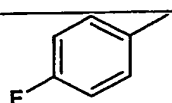
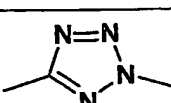
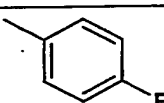
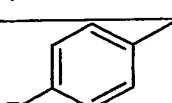
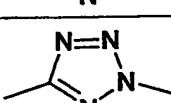
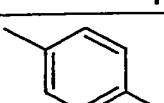
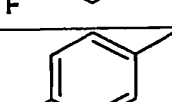
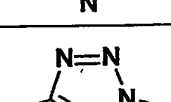
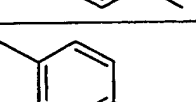
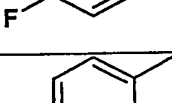
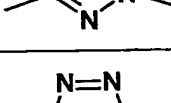
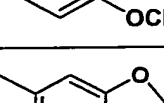
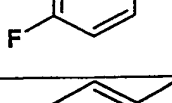
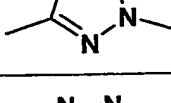
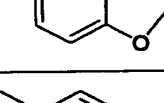
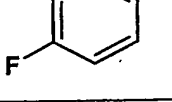
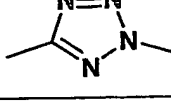
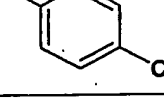
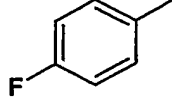
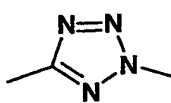
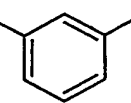
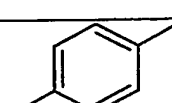
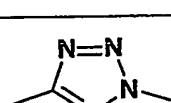
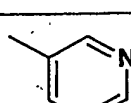
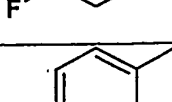
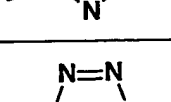
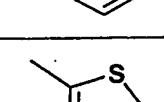
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

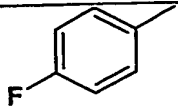
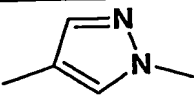
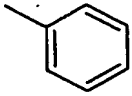
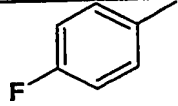
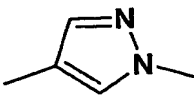
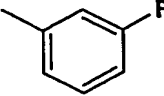
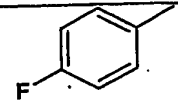
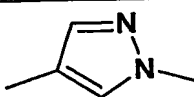
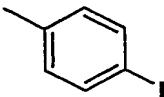
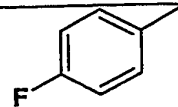
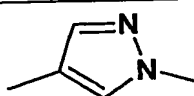
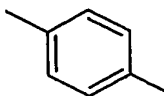
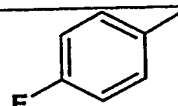
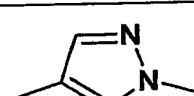
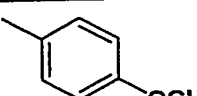
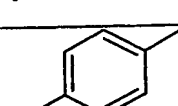
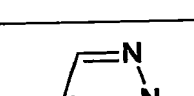
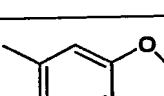
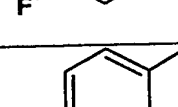
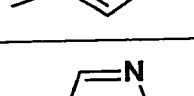
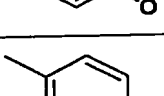
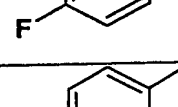
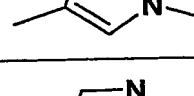
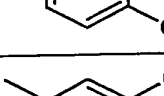
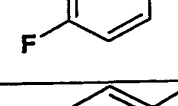
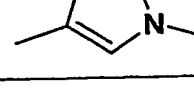
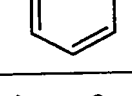
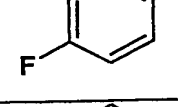
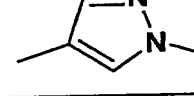
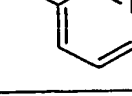
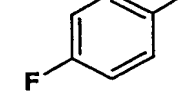
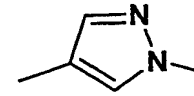
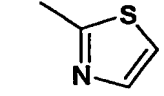
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):.

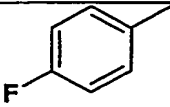
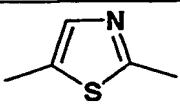
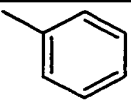
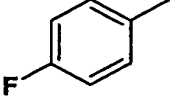
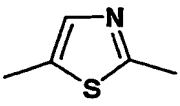
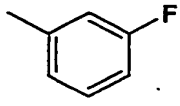
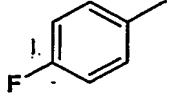
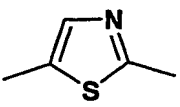
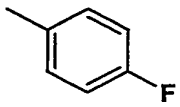
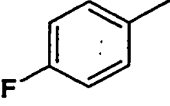
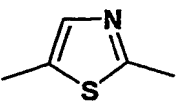
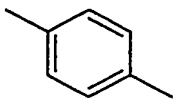
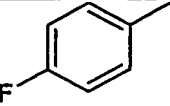
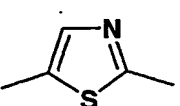
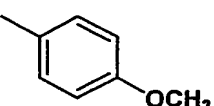
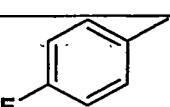
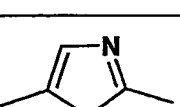
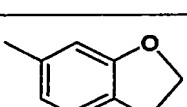
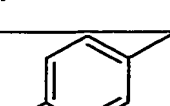
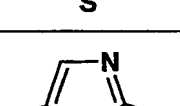
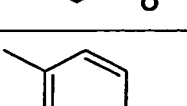
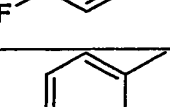
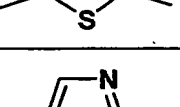
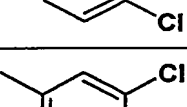
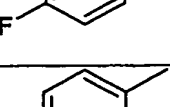
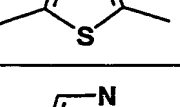
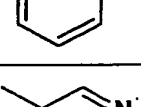
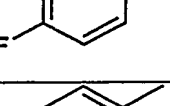
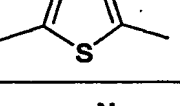
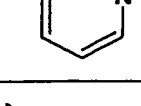
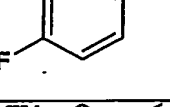
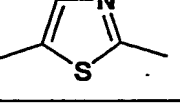
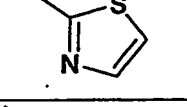
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

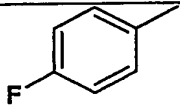
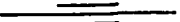
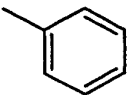
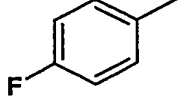

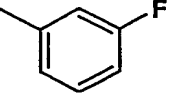
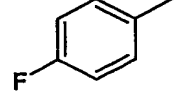

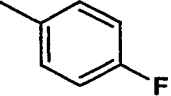
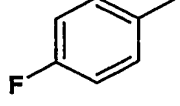
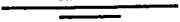
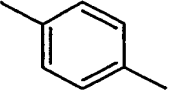
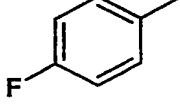
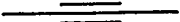
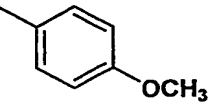
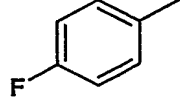
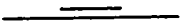
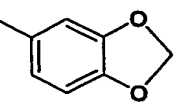
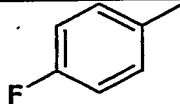

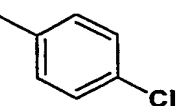
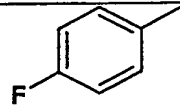

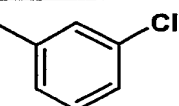
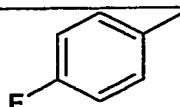

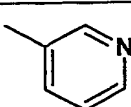
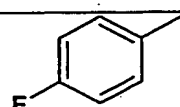

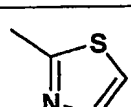
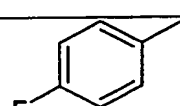

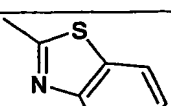
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

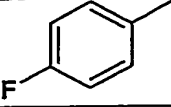

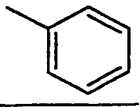
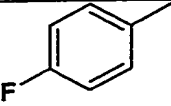
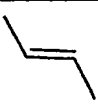
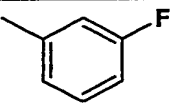
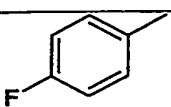

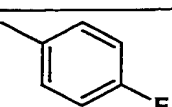
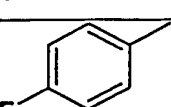

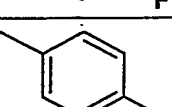
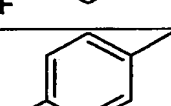

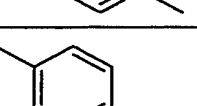
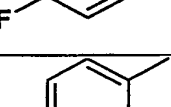
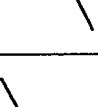
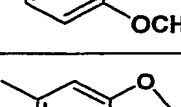
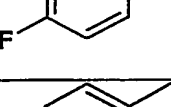

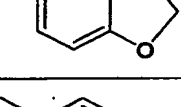
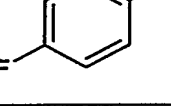
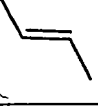
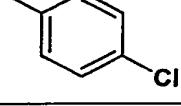
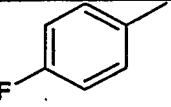
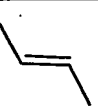
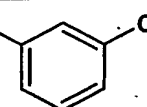
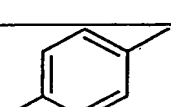

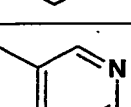
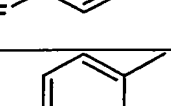

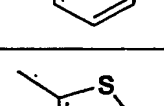
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

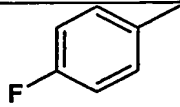
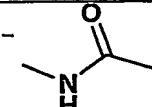
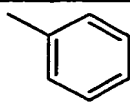
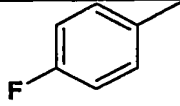
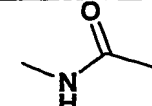
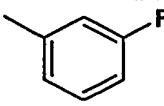
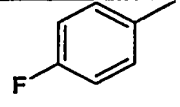
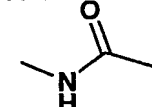
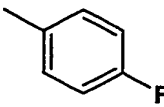
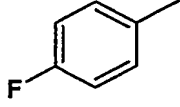
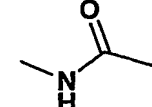
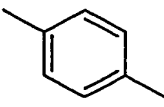
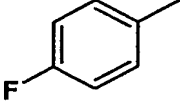
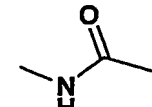
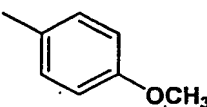
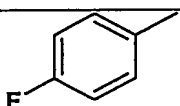
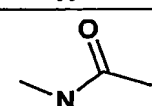
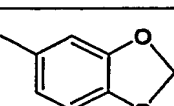
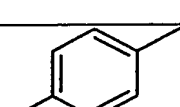
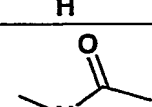
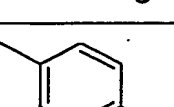
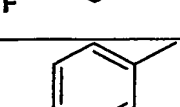
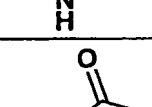
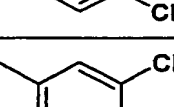
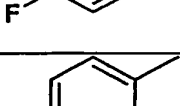
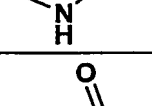
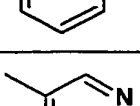
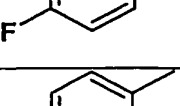
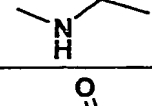
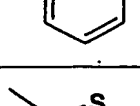
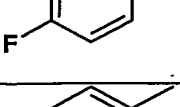
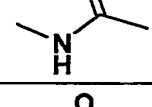
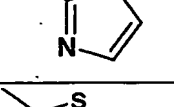
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

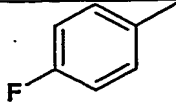
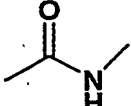
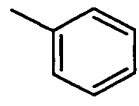
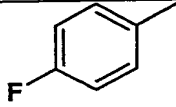
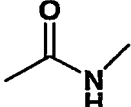
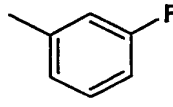
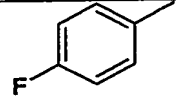
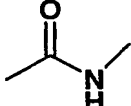
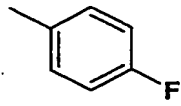
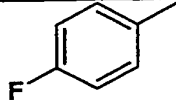
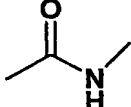
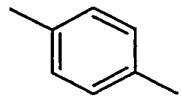
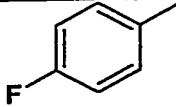
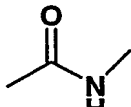
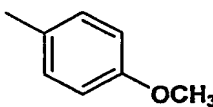
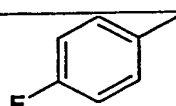
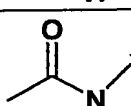
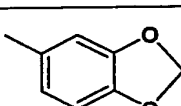
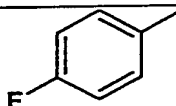
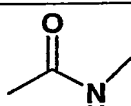
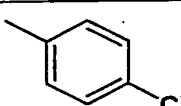
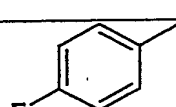
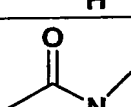
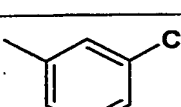
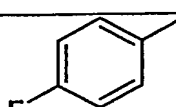
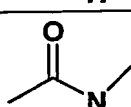
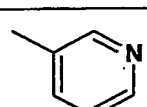
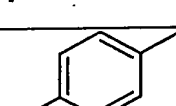
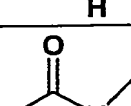
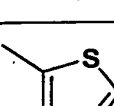
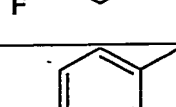
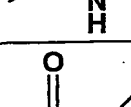
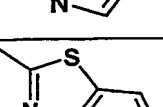
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

P	A	Q

TABLE I (continued):

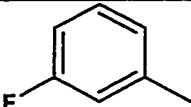
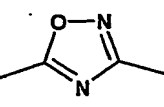
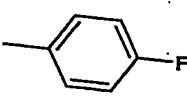
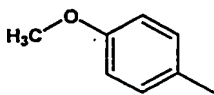
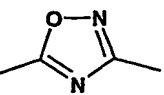
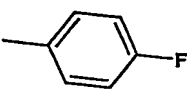
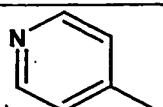
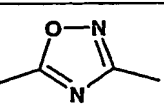
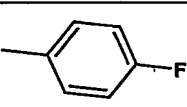
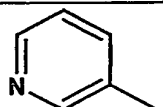
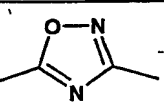
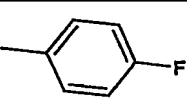
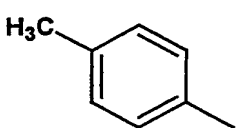
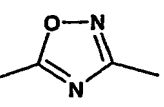
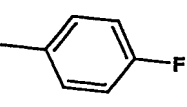
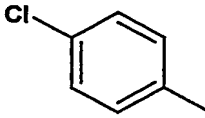
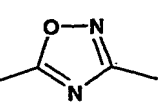
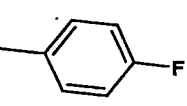
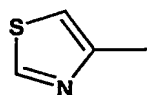
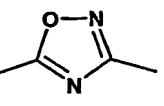
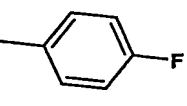
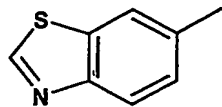
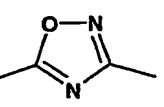
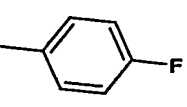
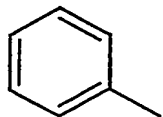
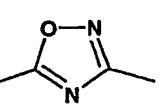
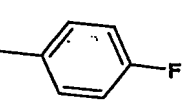
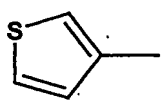
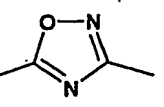
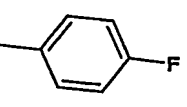
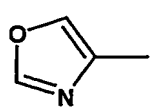
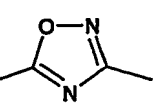
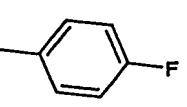
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

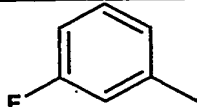
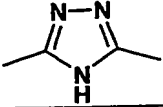
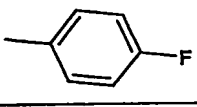
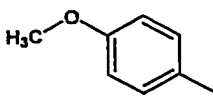
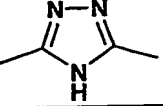
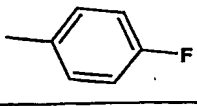
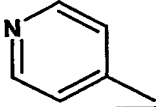
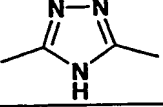
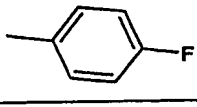
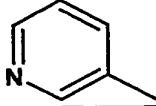
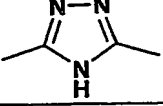
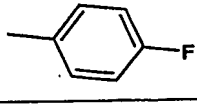
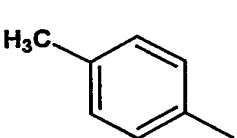
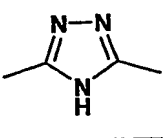
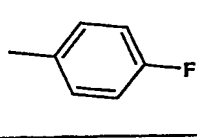
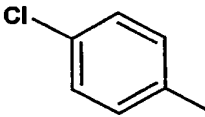
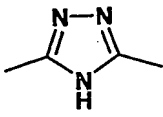
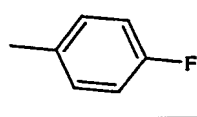
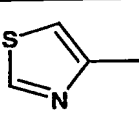
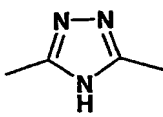
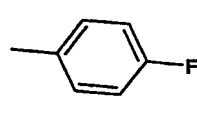
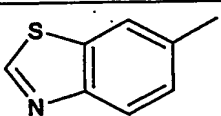
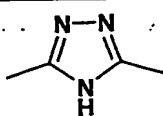
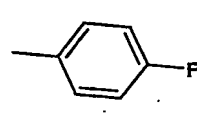
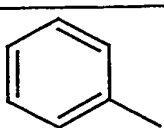
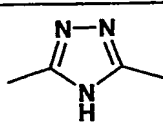
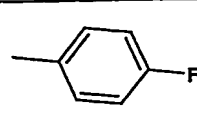
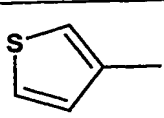
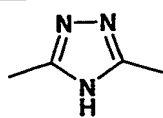
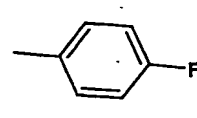
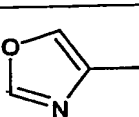
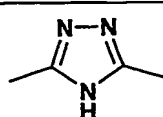
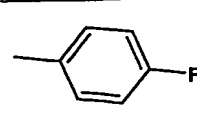
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

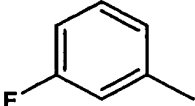
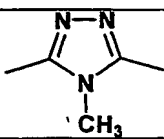
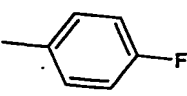
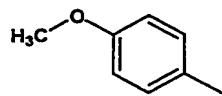
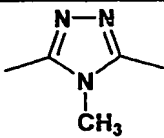
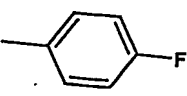
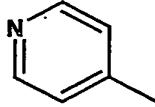
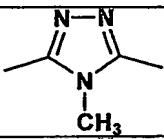
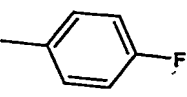
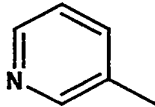
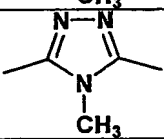
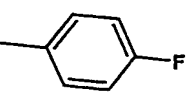
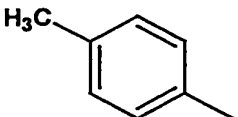
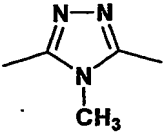
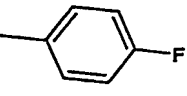
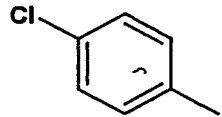
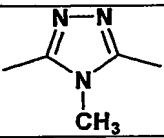
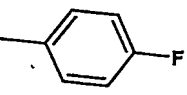
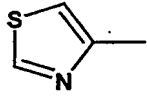
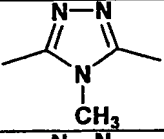
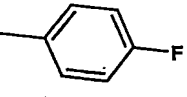
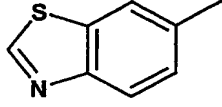
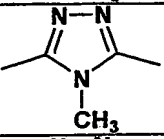
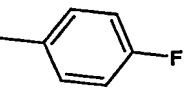
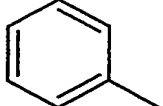
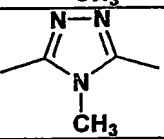
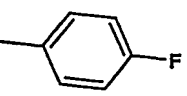
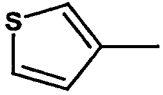
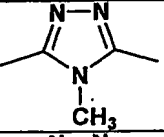
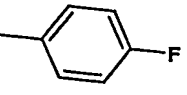
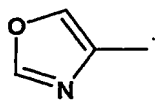
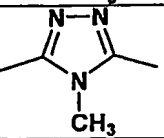
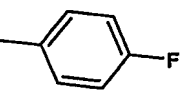
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

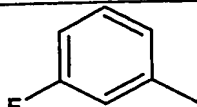
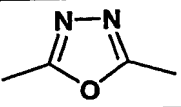
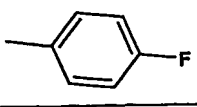
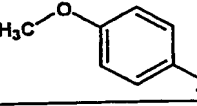
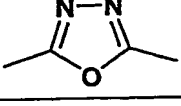
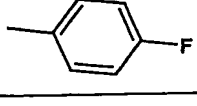
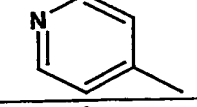
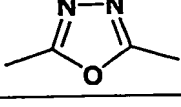
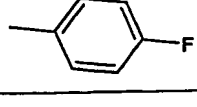
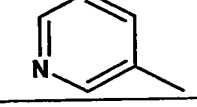
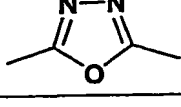
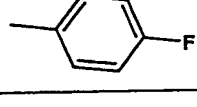
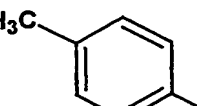
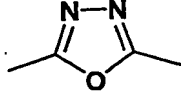
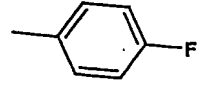
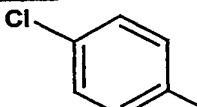
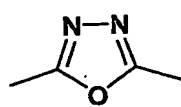
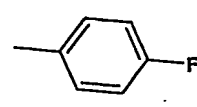
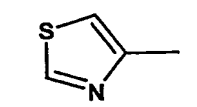
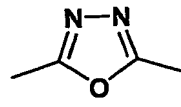
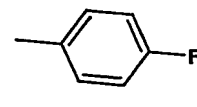
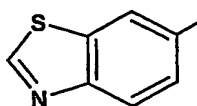
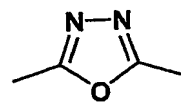
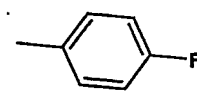
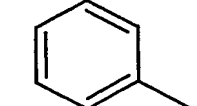
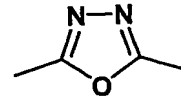
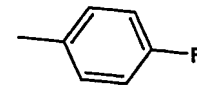
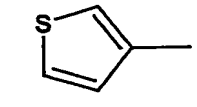
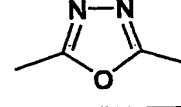
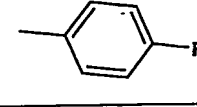
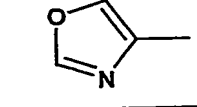
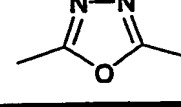
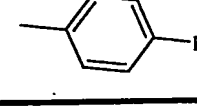
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

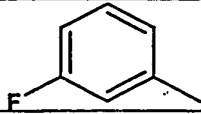
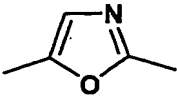
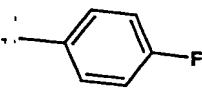
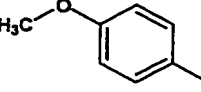
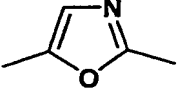
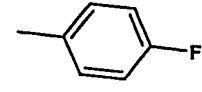
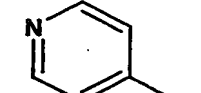
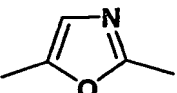
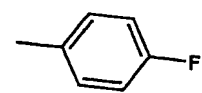
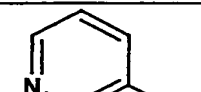
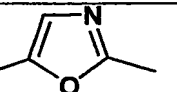
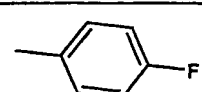
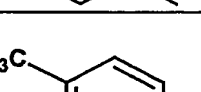
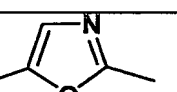
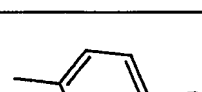
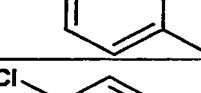
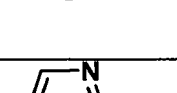
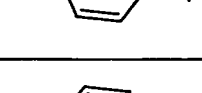
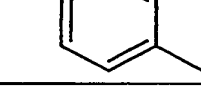
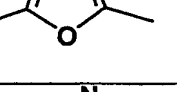
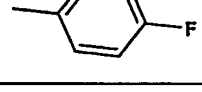
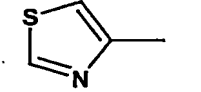
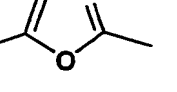
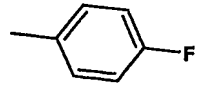
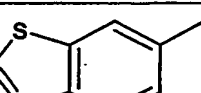
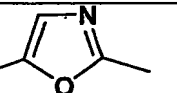
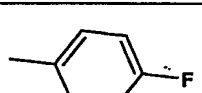
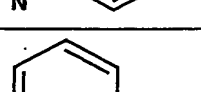
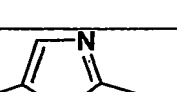

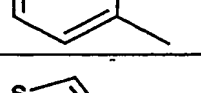
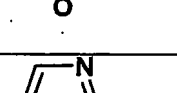
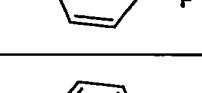
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

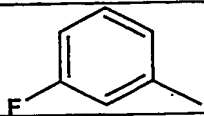
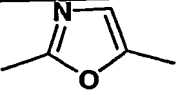
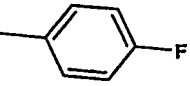
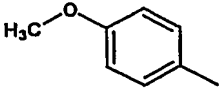
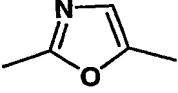
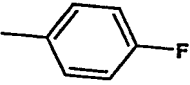
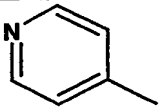
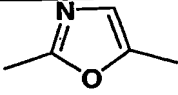
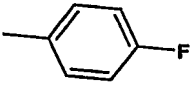
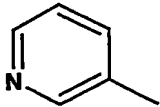
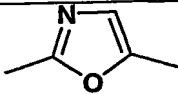
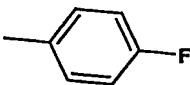
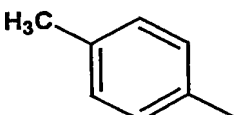
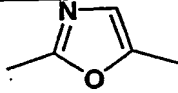
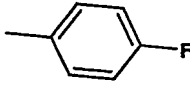
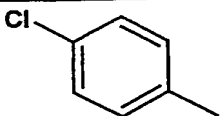
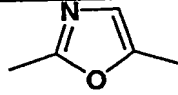
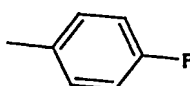
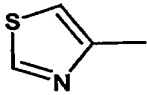
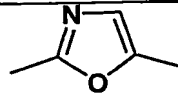
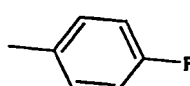
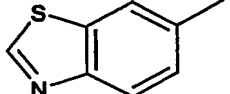
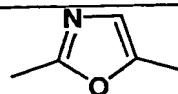
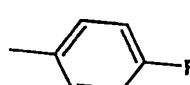
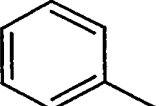
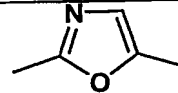
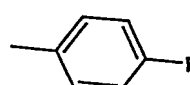
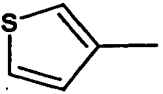
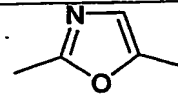
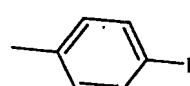
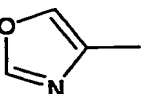
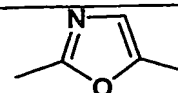
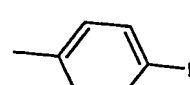
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

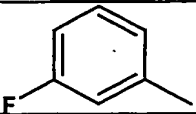
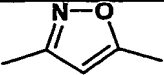
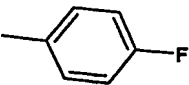
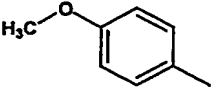

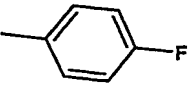
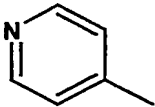
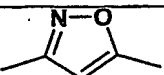
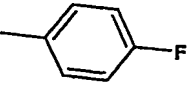
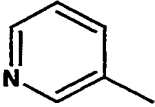
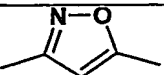
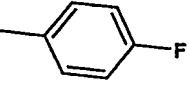
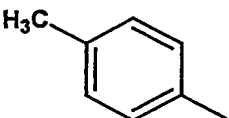
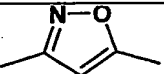
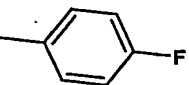
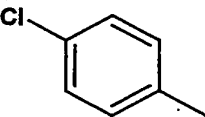
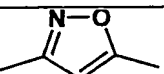
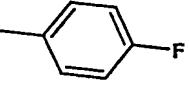
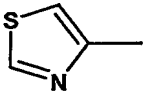
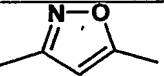
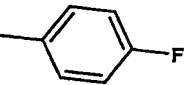
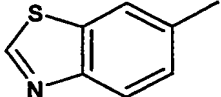
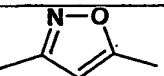
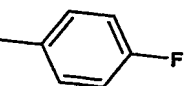
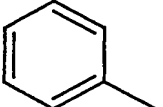
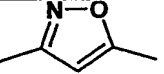
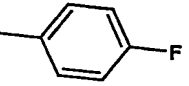
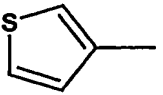
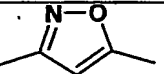
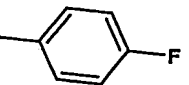
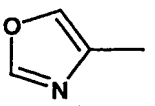
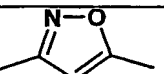
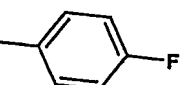
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

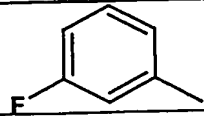
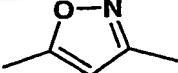
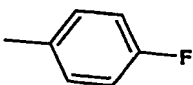
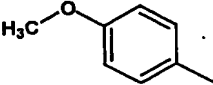
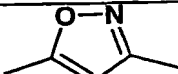
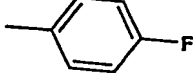
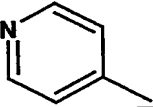
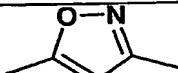
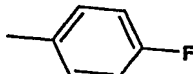
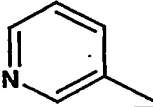
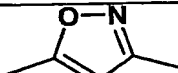
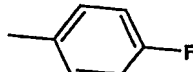
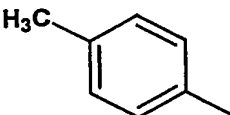
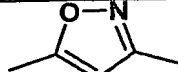
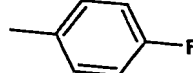
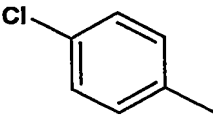
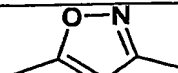
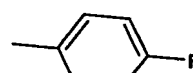
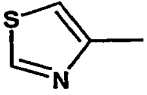
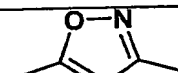
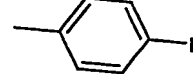
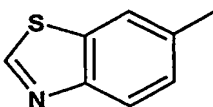
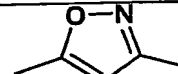
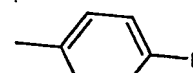
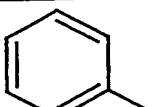
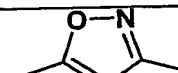
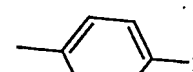
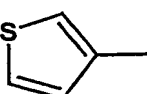
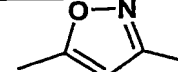
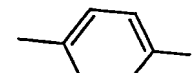
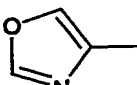
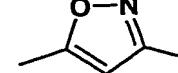
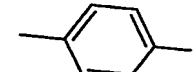
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

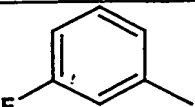
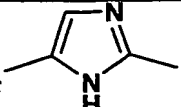
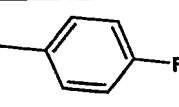
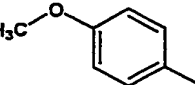
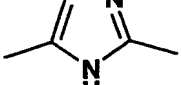
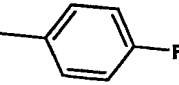
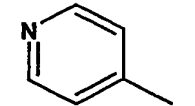
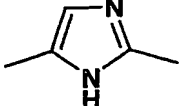
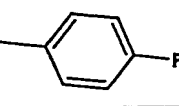
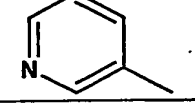
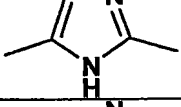
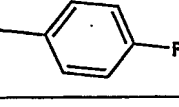
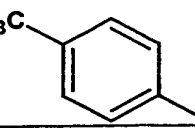
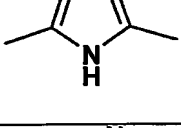
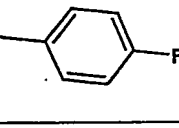
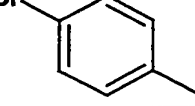
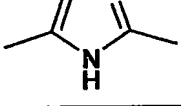
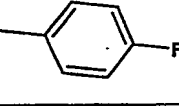
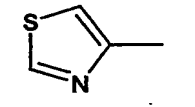
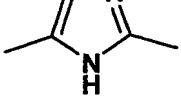
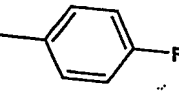
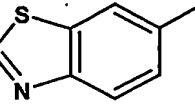
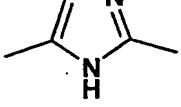
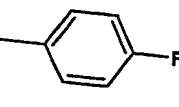
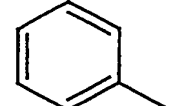
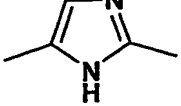
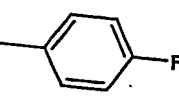
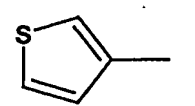
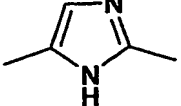
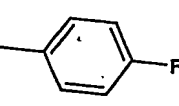
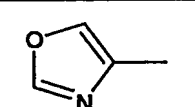
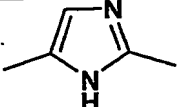
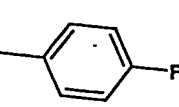
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

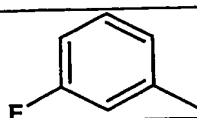
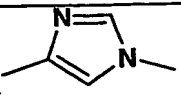
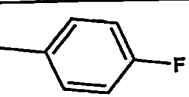
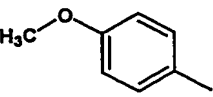
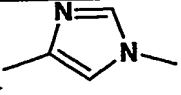
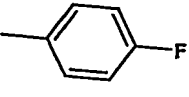
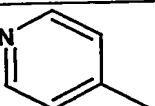
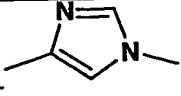
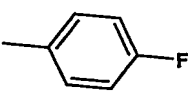
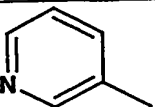
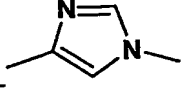
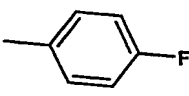
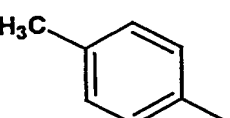
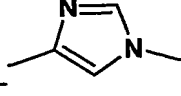
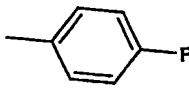
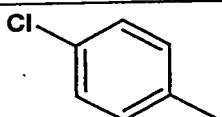
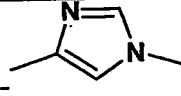
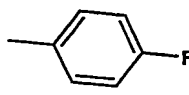
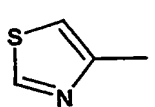
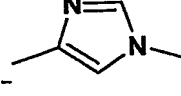
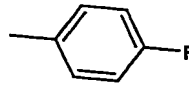
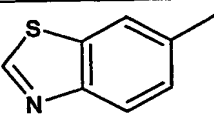
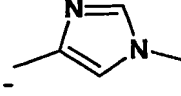
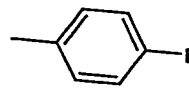
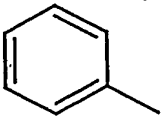
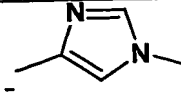
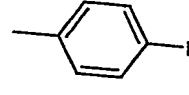
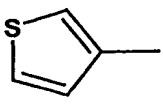
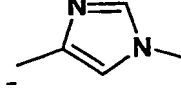
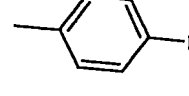
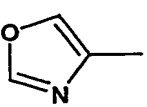
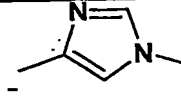
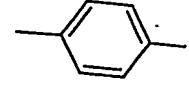
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

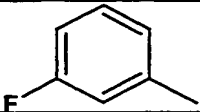
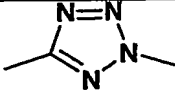
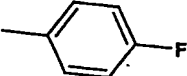
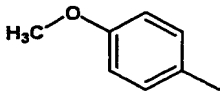
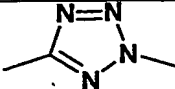
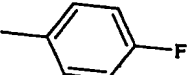
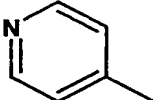
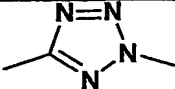
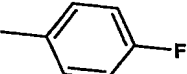
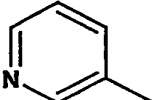
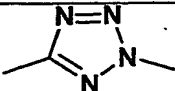
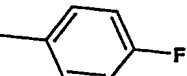
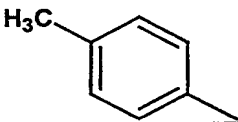
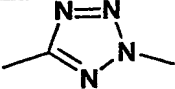
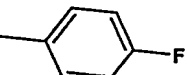
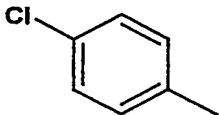
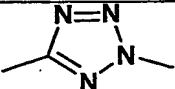
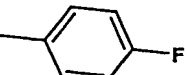
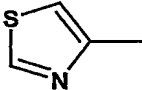
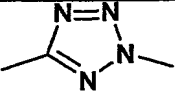
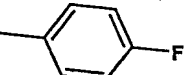
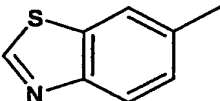
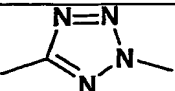
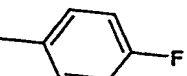
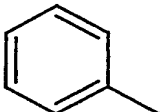
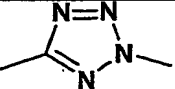
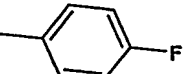
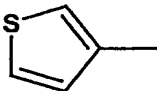
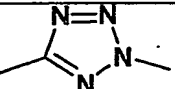
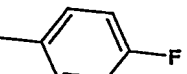
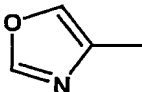
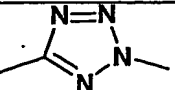
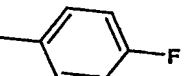
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

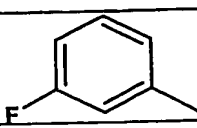
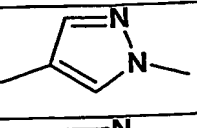
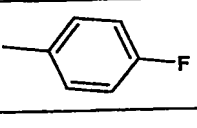
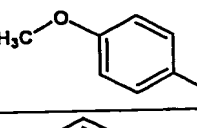
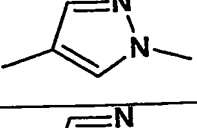
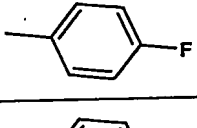
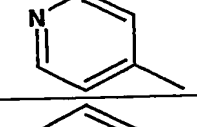
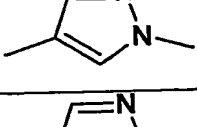
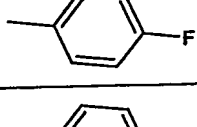
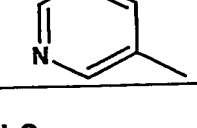
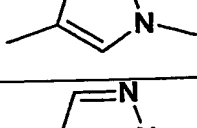
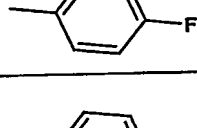
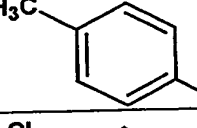
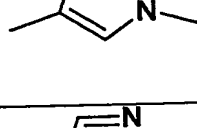
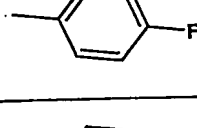
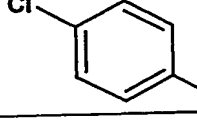
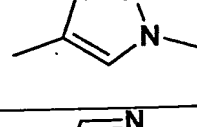
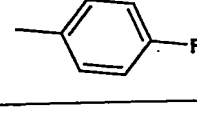
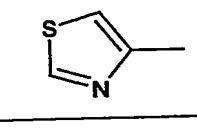
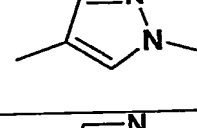
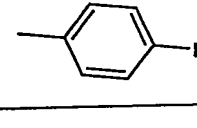
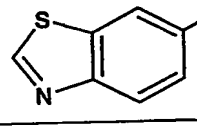
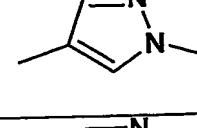
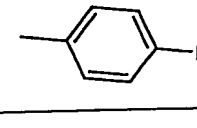
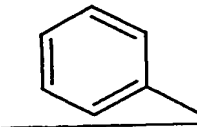
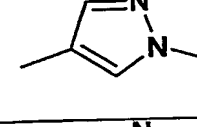
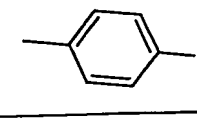
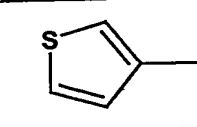
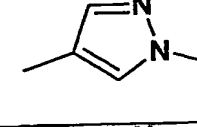
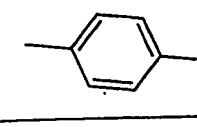
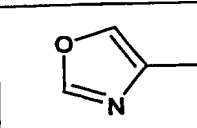
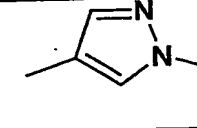
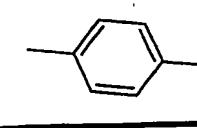
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

P	A	Q

TABLE I (continued)

P	A	Q

TABLE I (continued):

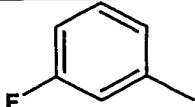

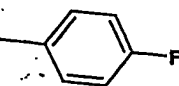
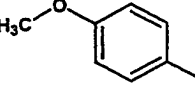

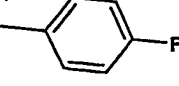
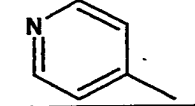

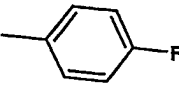
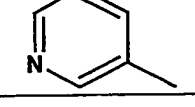

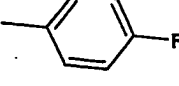
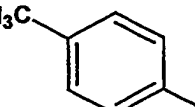

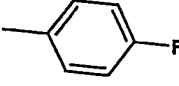
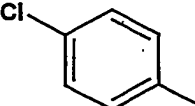

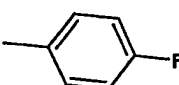
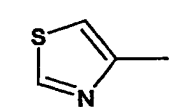

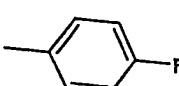
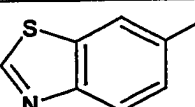

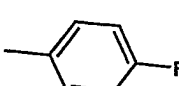
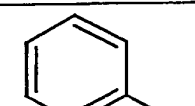

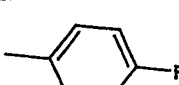
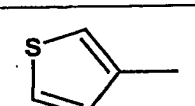

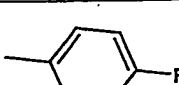
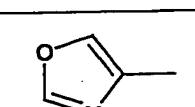

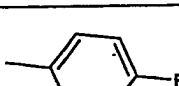
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

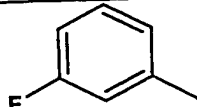
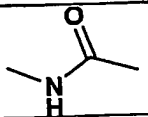
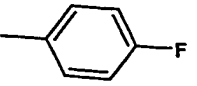
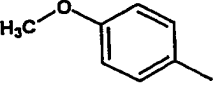
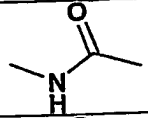
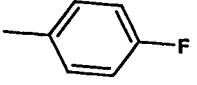
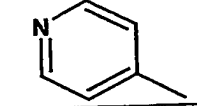
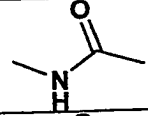
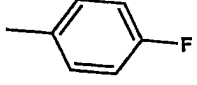
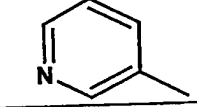
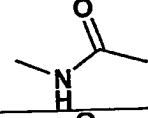
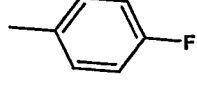
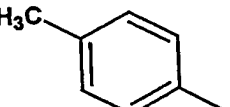
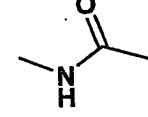
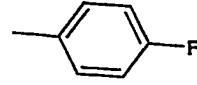
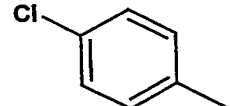
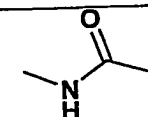
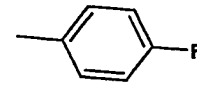
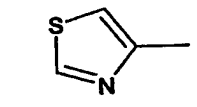
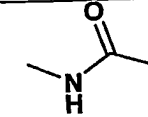
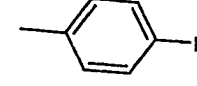
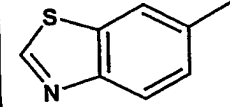
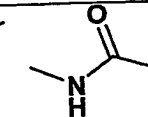
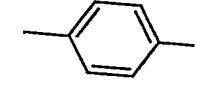
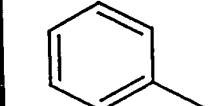
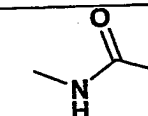
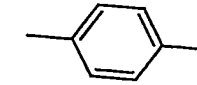
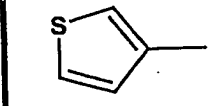
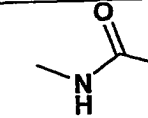
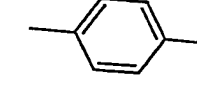
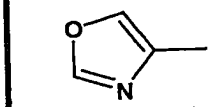
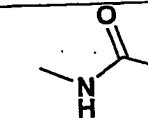
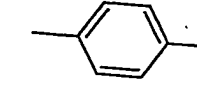
P	A	Q
		
		
		
		
		
		
		
		
		
		
		

TABLE I (continued):

P	A	Q

Specifically preferred compounds are:

{3-[3-(4-Methoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-phenyl-
 methanone
 {3-[3-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-phenyl-methanone
 (4-Fluoro-phenyl)-[3-(3-phenyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-methanone
 (3-Fluoro-phenyl)-[3-(3-phenyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-methanone
 (4-Fluoro-phenyl)-{3-[3-(3-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-
 methanone
 (3-Fluoro-phenyl)-{3-[3-(3-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-
 methanone
 (4-Fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-
 methanone
 (3-Fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-
 methanone
 (4-Fluoro-phenyl)-[3-(4-fluoro-phenylethynyl)-piperidin-1-yl]-methanone
 (4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-4H-[1,2,4]triazol-3-yl]-piperidin-1-yl}-
 methanone
 (R)-(4-Fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-
 yl}-methanone
 (S)-(4-Fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-
 yl}-methanone
 (4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-
 methanone
 (4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-
 piperidin-1-yl}-methanone
 (4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-piperidin-1-yl}-
 methanone
 (4-Fluoro-phenyl)-{3-[2-(4-fluoro-phenyl)-oxazol-5-yl]-piperidin-1-yl}-methanone
 (4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-oxazol-2-yl]-piperidin-1-yl}-methanone
 (4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-thiazol-2-yl]-piperidin-1-yl}-methanone
 (4-Fluoro-phenyl)-{3-[2-(4-fluoro-phenyl)-thiazol-5-yl]-piperidin-1-yl}-methanone
 (4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-[1,3,4]thiadiazol-2-yl]-piperidin-1-yl}-
 methanone

The present invention relates to the pharmaceutically acceptable acid addition salts of compounds of the formula (I) or pharmaceutically acceptable carriers or excipients.

The present invention relates to a method of treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGLUR5 allosteric modulators and particularly positive allosteric modulators.

The present invention relates to a method useful for treating or preventing peripheral and central nervous system disorders selected from the group consisting of: tolerance

or dependence, anxiety, depression, psychiatric disease such as psychosis, inflammatory or neuropathic pain, memory impairment, Alzheimer's disease, ischemia, drug abuse and addiction.

The present invention relates to pharmaceutical compositions which provide from about 0.01 to 1000 mg of the active ingredient per unit dose. The compositions may be administered by any suitable route. For example orally in the form of capsules, etc..., parenterally in the form of solutions for injection, topically in the form of ointments or lotions, ocularly in the form of eye-lotion, rectally in the form of suppositories.

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art; the nature of the pharmaceutical composition employed will depend on the desired route of administration. The total daily dose usually ranges from about 0.05 – 2000 mg.

METHODS OF SYNTHESIS

Compounds of general formula I may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthesis schemes. In all of the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T.W. Green and P.G.M. Wuts (1991) *Protecting Groups in Organic Synthesis*, John Wiley et Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of process as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of formula I.

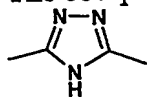
The compound of formula I may be represented as a mixture of enantiomers, which may be resolved into the individual pure *R*- or *S*-enantiomers. If for instance, a particular enantiomer of the compound of formula I is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provided the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group such as amino, or an acidic functional group such as carboxyl, this resolution may be conveniently performed by fractional crystallization from various solvents, of the salts of the compounds of formula I with optical active acid or by other methods known in the literature, e.g. chiral column chromatography.

Resolution of the final product, an intermediate or a starting material may be performed by any suitable method known in the art as described by E.L. Eliel, S.H. Wilen and L.N. Mander (1984) *Stereochemistry of Organic Compounds*, Wiley-Interscience.

Many of the heterocyclic compounds of formula I where A is an heteroaromatic group can be prepared using synthetic routes well known in the art (A. R. Katritzky A.R. and C. W. Rees (1984) *Comprehensive Heterocyclic Chemistry*, Pergamon Press).

The product from the reaction can be isolated and purified employing standard techniques, such as extraction, chromatography, crystallization, distillation, and the like.

The compounds of formula I-A in the case with A is a triazole group of formula

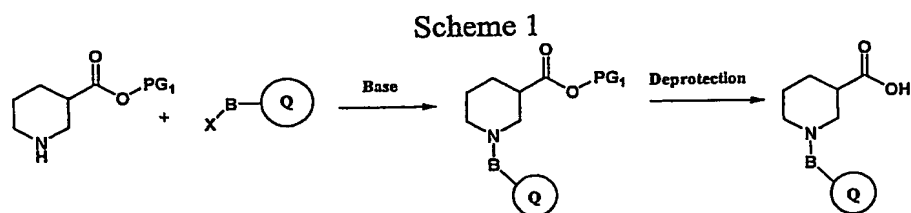


and W is a 3-substituted piperidine ring may be prepared according to the synthetic sequences illustrated in the Schemes 1-3.

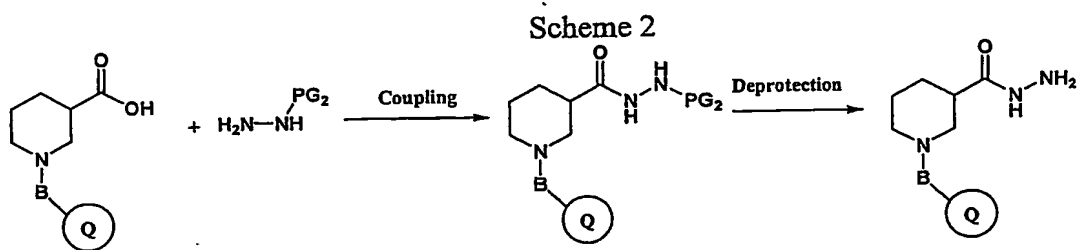
Wherein

P and Q each independently is aryl or heteroaryl as described above

B represents $-C(=O)-C_0-C_2\text{-alkyl-}$; $-S(=O)_2-C_0-C_2\text{-alkyl-}$.



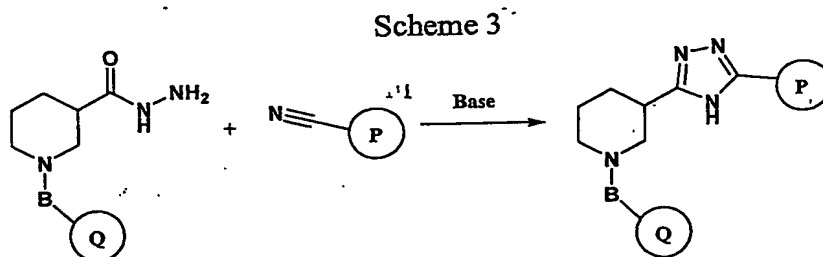
In the Scheme1, a nipecotic acid precursor (for example ethyl nipecotate) is reacted with an aryl or heteroaryl derivatives, for example 4-Fluoro-benzoyl chloride using method that are readily apparent to those skilled in the art. In a Scheme 1, B is as defined above, X is halogen, PG_1 is a protecting group such as benzyl, tbutyl, ethyl, allyl and the like. The reaction may be promoted by a base such as triethylamine, diisopropylamine, pyridine in a suitable solvent (e.g. tetrahydrofuran, dichloromethane) The reaction typically proceeds by allowing the reaction temperature to warm slowly from 0°C up to ambient temperature for a time in the range of about 4 up to 12hours. Protecting groups PG_1 are removed using conventional methods.



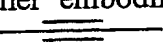
In turn, the substituted acid derivative (described in the scheme 1) may be converted to a hydrazide derivative using the approach outlined in the Scheme 2. In the Scheme 2, PG_2 is an amino protecting group such as tButyloxycarbonyl, Benzyloxycarbonyl, Ethoxycarbonyl, Benzyl and the like. The reaction may be promoted by coupling agent known in the art of organic synthesis such as EDCI (1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide), DCC (N,N'-Dicyclohexylcarbodiimide), in a suitable solvent (e.g. tetrahydrofuran, dichloromethane, N,N-dimethylformamide, Dioxane) Typically, a co-catalyst such as HOBT (Hydroxybenzotriazole) will also be present in the reaction mixture. The reaction

typically proceeds at ambient temperature for a time in the range of about 4 up to 12 hours. Protecting group PG₂ is removed using conventional methods.

Scheme 3 illustrates the final synthetic step.

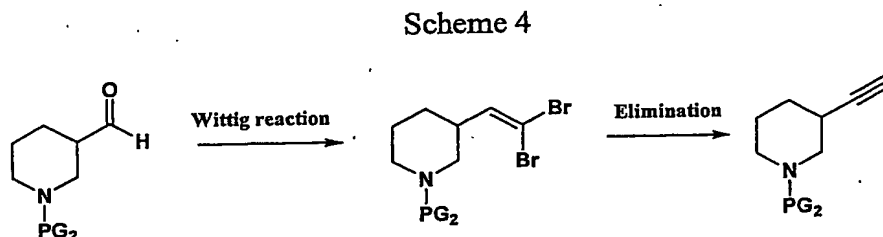


The derivatized hydrazide is reacted with a nitrile derivative (for example 4-Fluoro-benzonitrile) under basic condition such as sodium methylate or sodium ethylate and the like in a suitable solvent (e.g. methyl alcohol, ethyl alcohol). The reaction typically proceeds by allowing the reaction temperature to warm slowly from ambient temperature to 65°C for a time in the range of about 24 hours up to 48 hours (see for example Alcalde, Ermitas; Gisbert, Maria; Perez-Garcia, Lluisa; Tetrahedron; 51; 48; 1995; 13365-13378).

In another embodiment of the invention, the compounds of formula I-A wherein A is  and W is a 3-substituted piperidine ring may be prepared according to the synthetic sequences illustrated in the Schemes 4-6.

Wherein

P and Q each independently is aryl or heteroaryl as described above
B represents -C(=O)-C₀-C₂-alkyl-, -S(=O)₂-C₀-C₂-alkyl-.



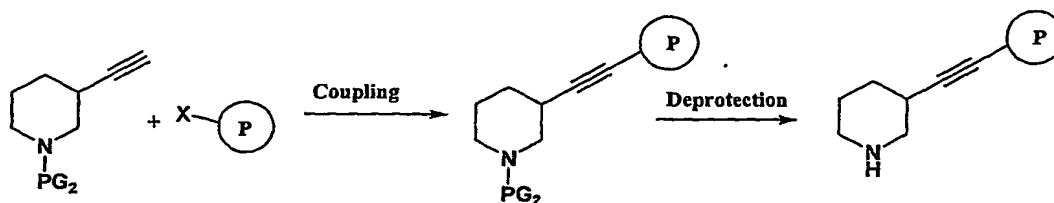
In accordance with the present invention, acetylenic derivatives can be prepared by methods known in the art, for example, by process described above. The free nitrogen of the piperidine moiety is protected with an amino protecting group PG₂.

An appropriate aldehyde derivative, for example 3-Formyl-piperidine-1-carboxylic acid tert-butyl ester is converted into the corresponding unsaturated gem-dibromide derivative in a Wittig reaction according to the method illustrated in the patent WO 02/088114. The Wittig reaction may be promoted by a mixture of methylene precursors (for example carbene tetrabromide) and a phosphine such as triphenylphosphine in a suitable solvent (e.g. dichloromethane, tetrahydrofuran, diethylether). If required a catalyst, such as zinc dust, will also be present in the reaction mixture. The reaction is typically allowed to proceed by maintaining at room temperature for a time in the range of about 12 hours up to 24 hours. The unsaturated

gem-dibromide compound is then reacted with an organometallic species such as *n*-butyllithium, *t*Butyllithium and the like which is capable of undergoing metal exchange reaction following by dehydrohalogenation reaction. The reaction may be promoted in suitable solvent (e.g. tetrahydrofuran, ether and the like) at a temperature between -78°C for 1 hour.

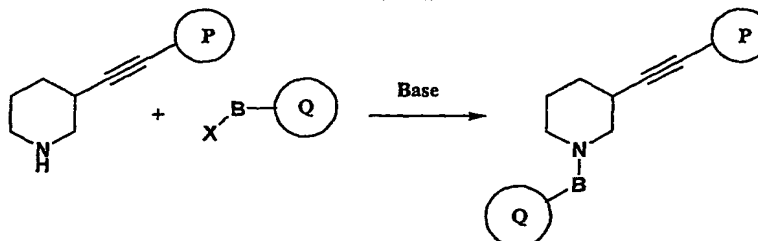
The scheme 5 illustrates the preparation of disubstituted acetylenic derivatives by reacting an alkyne derivative (described in the Scheme 4), for example 3-Ethynyl-piperidine-1-carboxylic acid *tert*-butyl ester, with a substituted P, for example 1-Fluoro-4-iodo-benzene. Thus in Scheme 5, X includes halides such as Cl, Br, I or trifluoromethanesulfonyl and paratoluenesulfonyl. Such general route of synthesis has been reported in *J. Med. Chem.* 2000, 43, 4288-4312.

Scheme 5

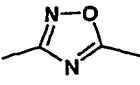


This palladium catalyzed C-C coupling reaction requires a catalyst such as $\text{PdCl}_2(\text{PPh}_3)_2$, $\text{Pd}(\text{PPh}_3)_4$, $\text{Pd}(\text{OAc})_2$ or Pd on carbon in a suitable solvent like DMF, acetonitrile or benzene. Typically a co-catalyst such as copper(I) iodide and a base (e.g., triethylamine, diisopropylamine, potassium acetate...) will also be present in the reaction mixture. The coupling reaction typically proceeds by allowing the reaction temperature to warm slowly from about 0° up to ambient temperature, or heated to a temperature anywhere between 30°C and 150°C . The reaction mixture is then maintained at a suitable temperature for a time in the range of about 1 up to 24 hours, with about 12 hours typically being sufficient. Protecting groups PG_2 are removed using standard methods.

Scheme 6



The scheme 6 illustrates the last step following a process similar to those described in scheme 1.

The compounds of formula I-A wherein A is  and W is a 3-substituted piperidine ring may be prepared according to the synthetic sequences illustrates in the Schemes 7-9.

Wherein

P and Q each independently is aryl or heteroaryl as described above
B represents $-C(=O)-C_0-C_2\text{-alkyl-}$; $-S(=O)_2-C_0-C_2\text{-alkyl-}$.

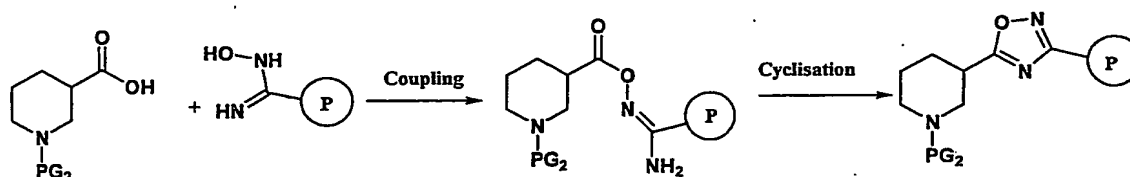
The starting material amidoxime can be prepared by methods known in the art of organic synthesis as set forth in part by the following synthesis scheme 7:

Scheme 7



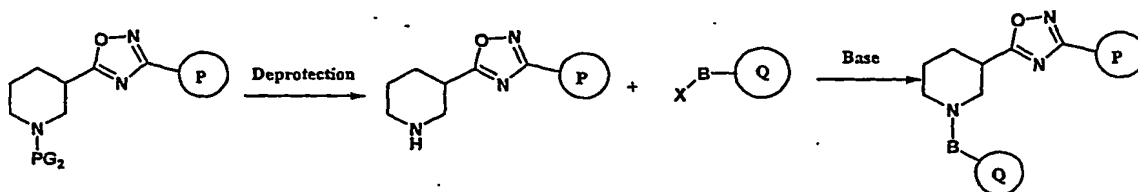
In the turn, an nitrile derivative (for example 4-Fluoro-benzonitrile) is reacted with hydroxylamine under basic condition such as triethylamine, diisopropylethylamine, sodium carbonate, sodium hydroxyde and the like in a suitable solvent (e.g. methyl alcohol, ethyl alcohol). The reaction typically proceeds by allowing the reaction temperature to warm slowly from ambient temperature to $80^\circ C$ for a time in the range of about 24 hours up to 48 hours (see for example Lucca, George V. De; Kim, Ui T.; Liang, Jing; Cordova, Beverly; Klabe, Ronald M.; et al; J.Med.Chem.; EN; 41; 13; 1998; 2411-2423, Lila, Christine; Gloanec, Philippe; Cadet, Laurence; Herve, Yolande; Fournier, Jean; et al.; Synth.Comm.; EN; 28; 23; 1998; 4419-4430).

Scheme 8

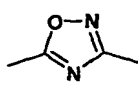


The substituted amidoxime derivative (described in the scheme 7) may be converted to an acyl-amidoxime derivative using the approach outlined in the Scheme 8. In the Scheme 8, PG_2 is a protecting group as defined above. The coupling reaction may be promoted by coupling agent known in the art of organic synthesis such as EDCI (1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide), DCC (N,N'-Dicyclohexylcarbodiimide), in a suitable solvent (e.g. tetrahydrofuran, dichloromethane, N,N-dimethylformamide, dioxane) Typically, a co-catalyst such as DMAP (N,N-dimethylaminopyridine) will also be present in the reaction mixture. The reaction typically proceeds at ambient temperature for a time in the range of about 4 hours up to 12 hours to produce the intermediate acyl-amidoxime. The cyclisation reaction may be effected thermally in a temperature range of about $80^\circ C$ up to about $150^\circ C$ for a time in the range of about 2 hours up to 12 hours (see for example Suzuki, Takeshi; Iwaoka, Kiyoshi; Imanishi, Naoki; Nagakura, Yukinori; Miyata, Keiji; et al.; Chem.Pharm.Bull.; EN; 47; 1; 1999; 120 - 122). The product from the reaction can be isolated and purified employing standard techniques, such as extraction, chromatography, crystallization, distillation, and the like.

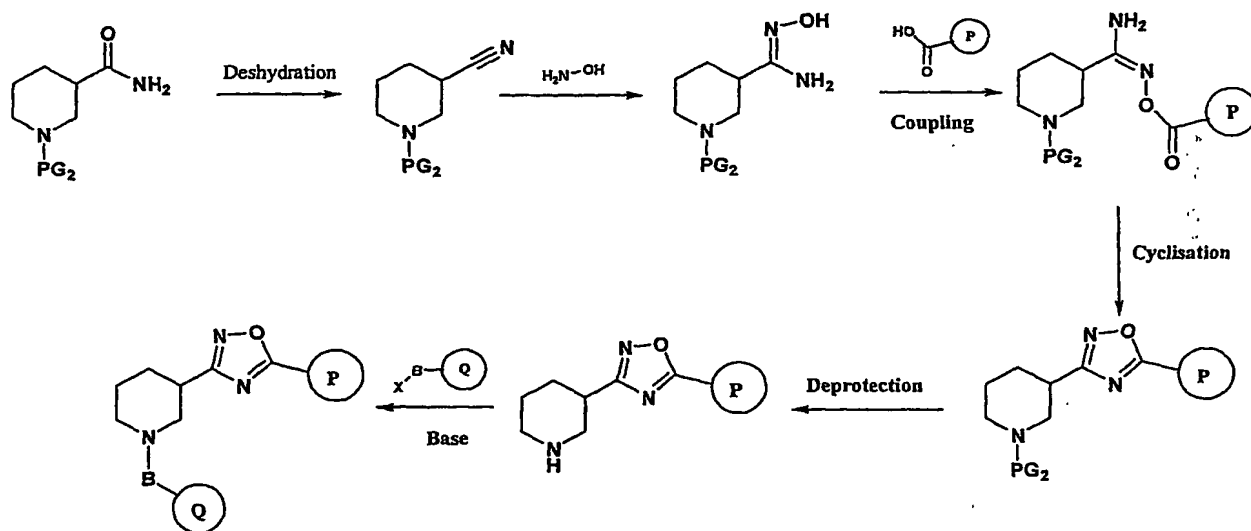
Scheme 9



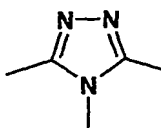
As shown in Scheme 9, protecting groups PG_2 are removed using standard methods. The coupling reaction illustrated in the scheme 9 is similar to those described in the Scheme 1.

The compounds of formula I-A in the case where A is a group of formula  and W is a 3-substituted piperidine ring may be prepared according to the synthetic sequences illustrated in the Scheme 10.

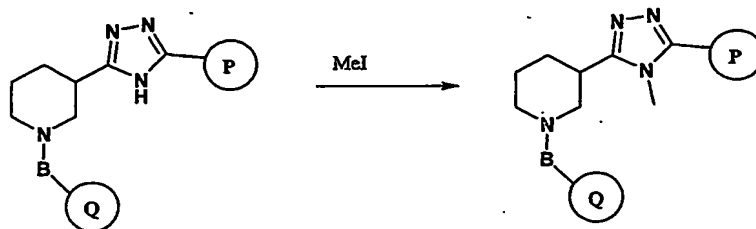
Scheme 10



The oxadiazole ring described above is prepared following synthetic routes well known in the art (A. R. Katritzky A.R. and C. W. Rees (1984) *Comprehensive Heterocyclic Chemistry*, Pergamon Press).

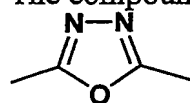
The compounds of formula I-A in the case where A is a group of formula  and W is a 3-substituted piperidine ring may be prepared according to the synthetic sequences illustrated in the Schemes 11.

Scheme 11



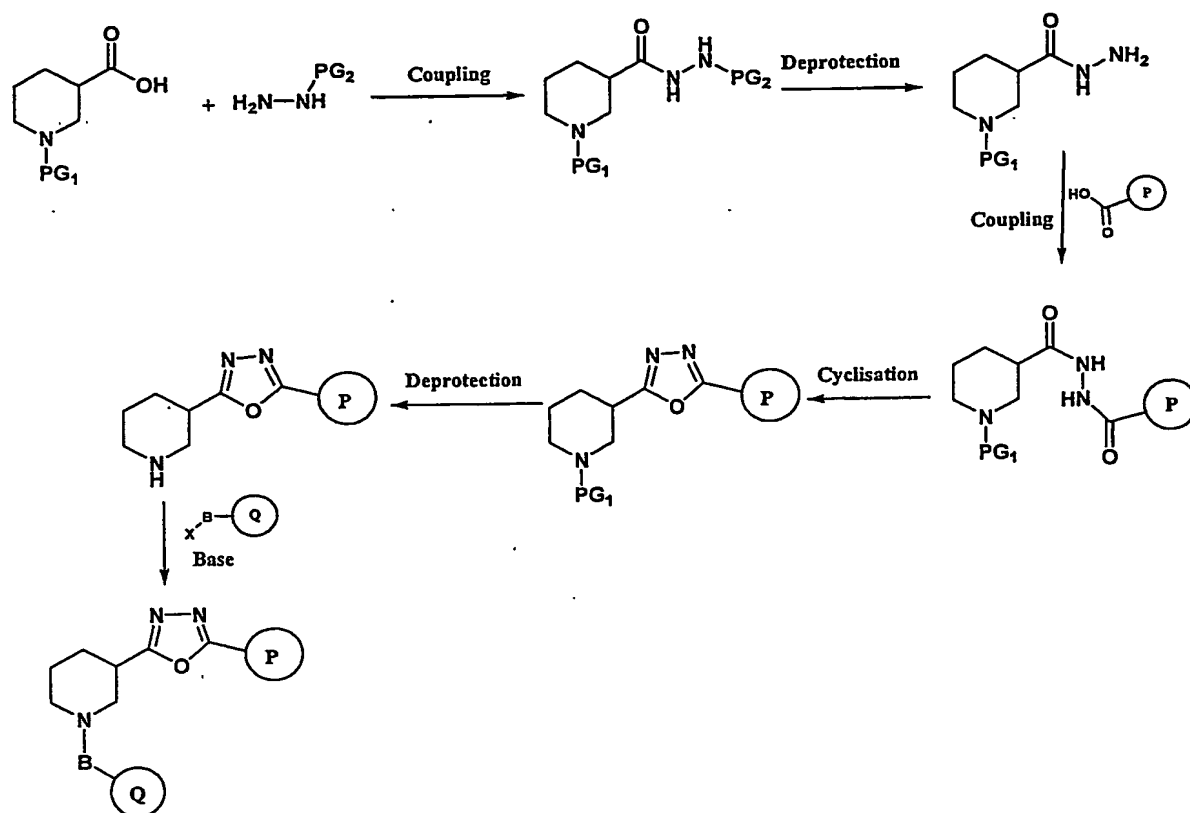
The alkylation of the triazole derivatives (described in the Scheme 1-3) with a alkylating agent such as Methyl iodide and the like under basic condition (e.g. NaH, MeONa and the like) afford the the N-Alkyl-triazole derivative (see for example Tarrago, Georges; Marzin, Claude; Najimi, Ouafa; Pellegrin, Valdo; J.Org.Chem.; 55; 2; 1990; 420-425).

The compounds of formula I-A in the case where A is a group of formula



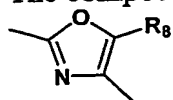
and W is a 3-substituted piperidine ring may be prepared according to the synthetic sequences illustrated in the Schemes 12.

Scheme 12



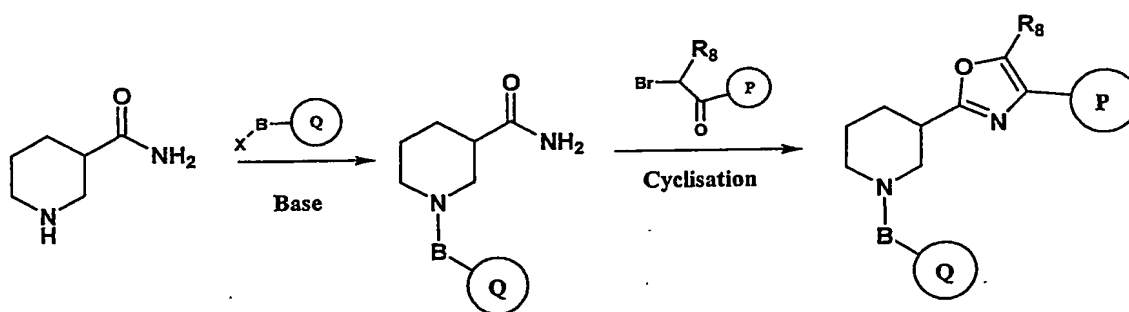
The oxadiazole ring describe above are prepared following synthetic routes well known in the art (A. R. Katrizky A.R. and C. W. Rees (1984) *Comprehensive Heterocyclic Chemistry*, Pergamon Press).

The compounds of formula I-A in the case where A is a group of formula

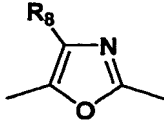


and W is a 3-substituted piperidine ring may be prepared according to the synthetic sequences illustrated in the Schemes 13.

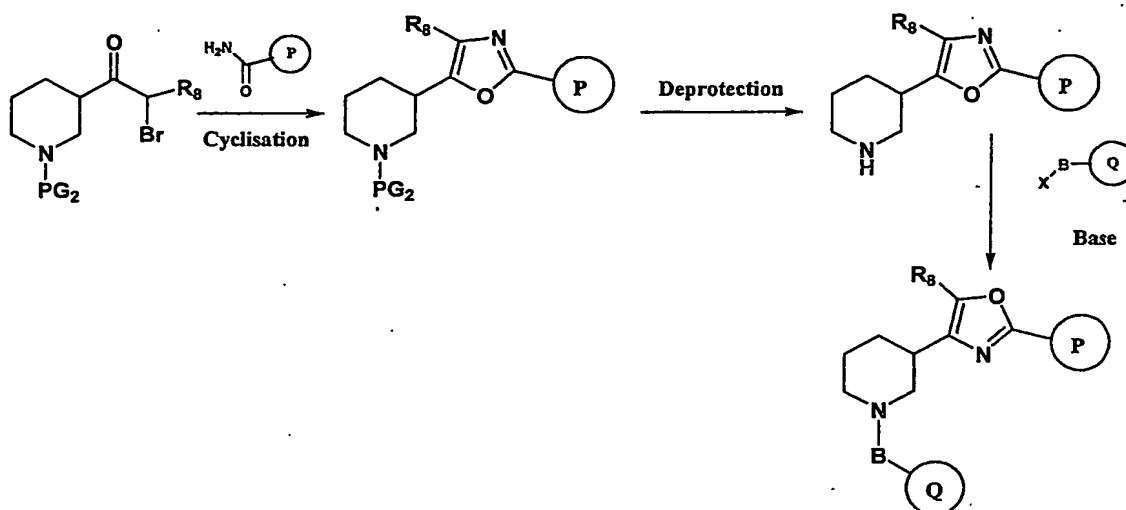
Scheme 13



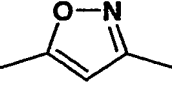
The oxazole ring describe above are prepared following synthetic routes well known in the art (A. R. Katrizky A.R. and C. W. Rees (1984) *Comprehensive Heterocyclic Chemistry*, Pergamon Press).

The compounds of formula I-A in the case with A is a group of formula  and W is a 3-substituted piperidine ring may be prepared according to the synthetic sequences illustrated in the Schemes 14.

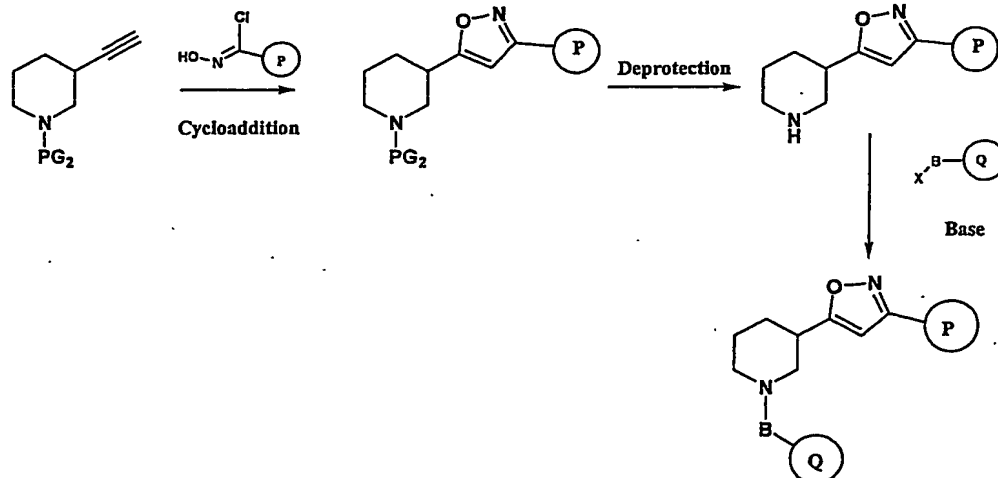
Scheme 14



The precursor α -Bromo-ketone derivatives described above are prepared according to synthetic routes well known in the art.

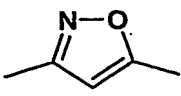
The compounds of formula I-A in the case with A is a group of formula  and W is a 3-substituted piperidine ring may be prepared according to the synthetic sequences illustrated in the Schemes 15.

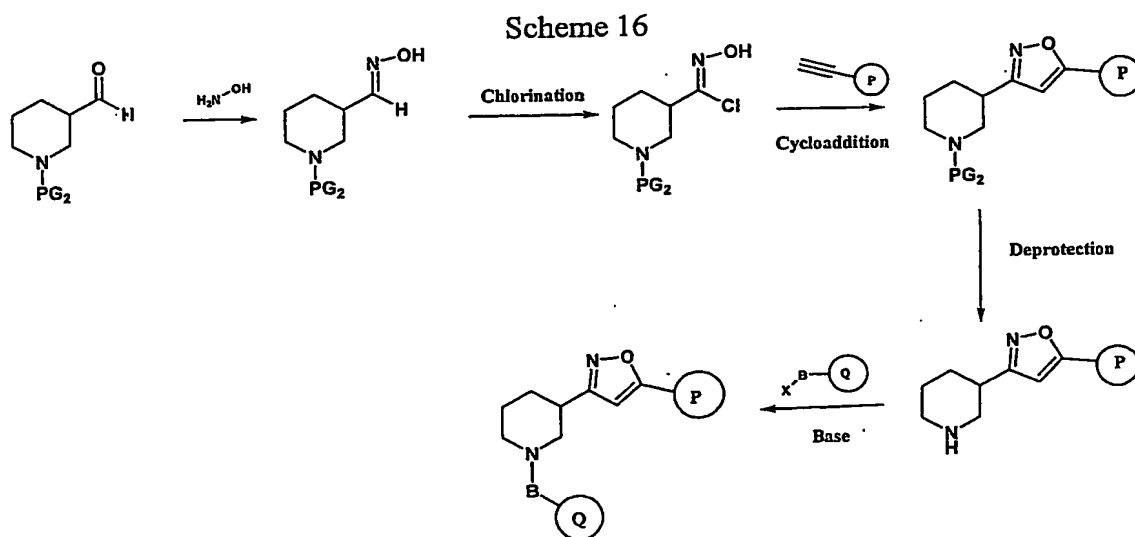
Scheme 15



Another embodiment of the present invention, a substituted acetylenic derivative (described in the scheme 4) may be converted to an oxazole derivative by reacting

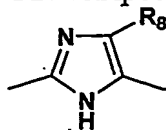
with an imino-chloride of aryl-oxime following synthetic routes well known in the art (see for example Diana, Guy D.; Volkots, Deborah L.; Nitz, Theodore J.; Bailey, Thomas R.; Long, Melody A.; et al.; J.Med.Chem.; 37; 15; 1994; 2421-2436.).

The compounds of formula I-A in the case with A is a group of formula  and W is a 3-substituted piperidine ring may be prepared according to the synthetic sequences illustrated in the Schemes 16.



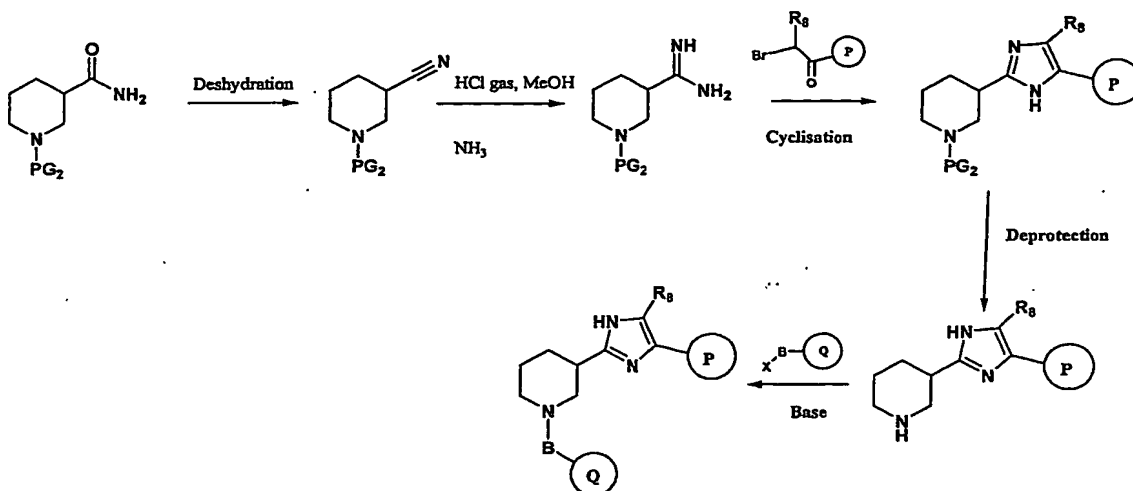
According to the present invention, a substituted acetylenic derivative may be converted to an oxazole derivative by reacting with an imino-chloride of aryl-oxime following synthetic routes well known in the art (see for example Diana, Guy D.; Volkots, Deborah L.; Nitz, Theodore J.; Bailey, Thomas R.; Long, Melody A.; et al.; J.Med.Chem.; 37; 15; 1994; 2421-2436.).

The compounds of formula I-A in the case where A is a group of formula



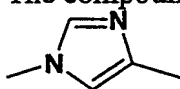
and W is a 3-substituted piperidine ring may be prepared according to the synthetic sequences illustrated in the Schemes 17.

Scheme 17



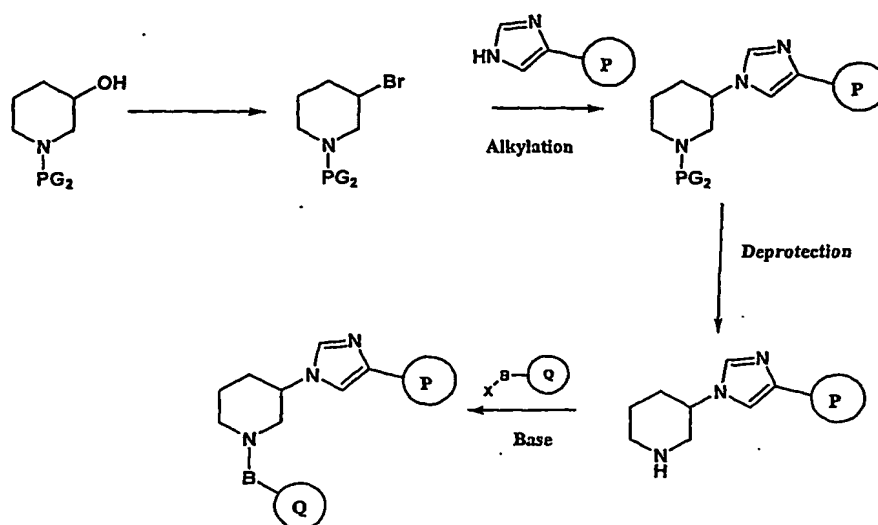
According to the present invention, a substituted amidine derivative may be converted to an imidazole derivative by reacting with an α -bromo-ketone following synthetic routes well known in the art (A. R. Katrizky A.R. and C. W. Rees (1984) *Comprehensive Heterocyclic Chemistry*, Pergamon Press).

The compounds of formula I-A in the case where A is a group of formula



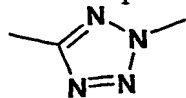
and W is a 3-substituted piperidine ring may be prepared according to the synthetic sequences illustrated in the Schemes 18.

Scheme 18



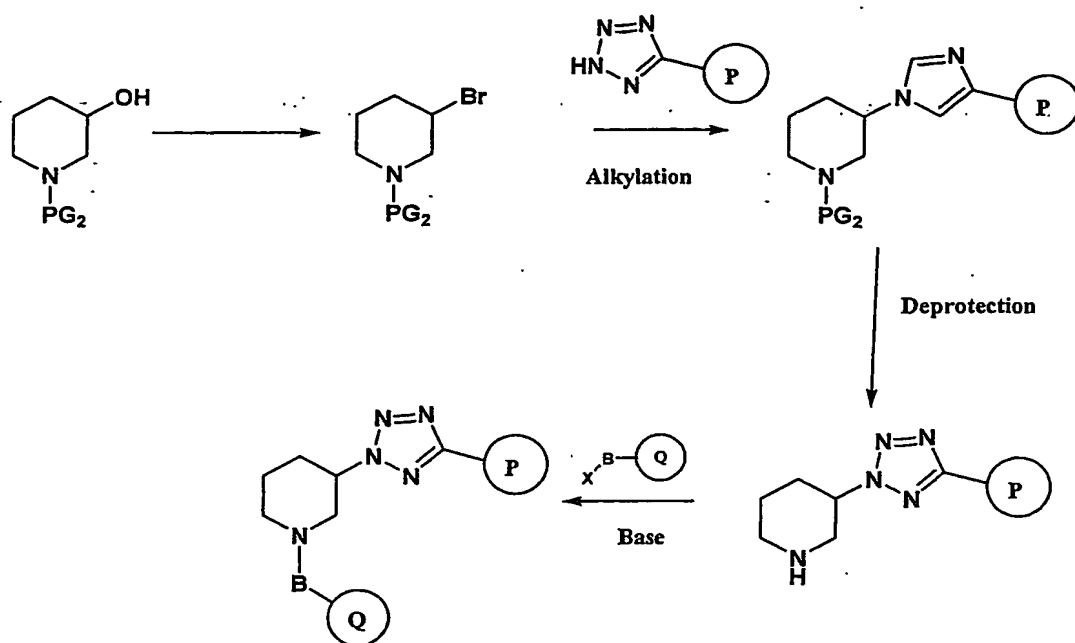
The precursor N-Aryl-imidazole derivatives are prepared according to synthetic routes well known in the art (A. R. Katrizky A.R. and C. W. Rees (1984) *Comprehensive Heterocyclic Chemistry*, Pergamon Press).

The compounds of formula I-A in the case where A is a group of formula



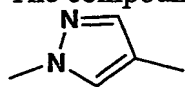
and W is a 3-substituted piperidine ring may be prepared according to the synthetic sequences illustrated in the Schemes 19.

Scheme 19



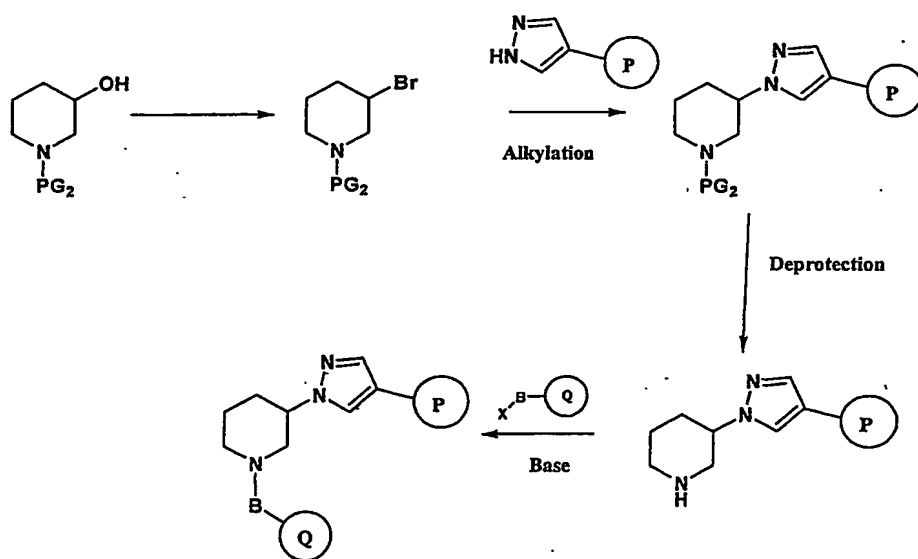
The precursor Aryl-tetrazole derivatives are prepared according to synthetic routes well known in the art (A. R. Katritzky A.R. and C. W. Rees (1984) *Comprehensive Heterocyclic Chemistry*, Pergamon Press).

The compounds of formula I-A in the case where A is a group of formula



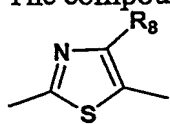
and W is a 3-substituted piperidine ring may be prepared according to the synthetic sequences illustrated in the Schemes 20.

Scheme 20



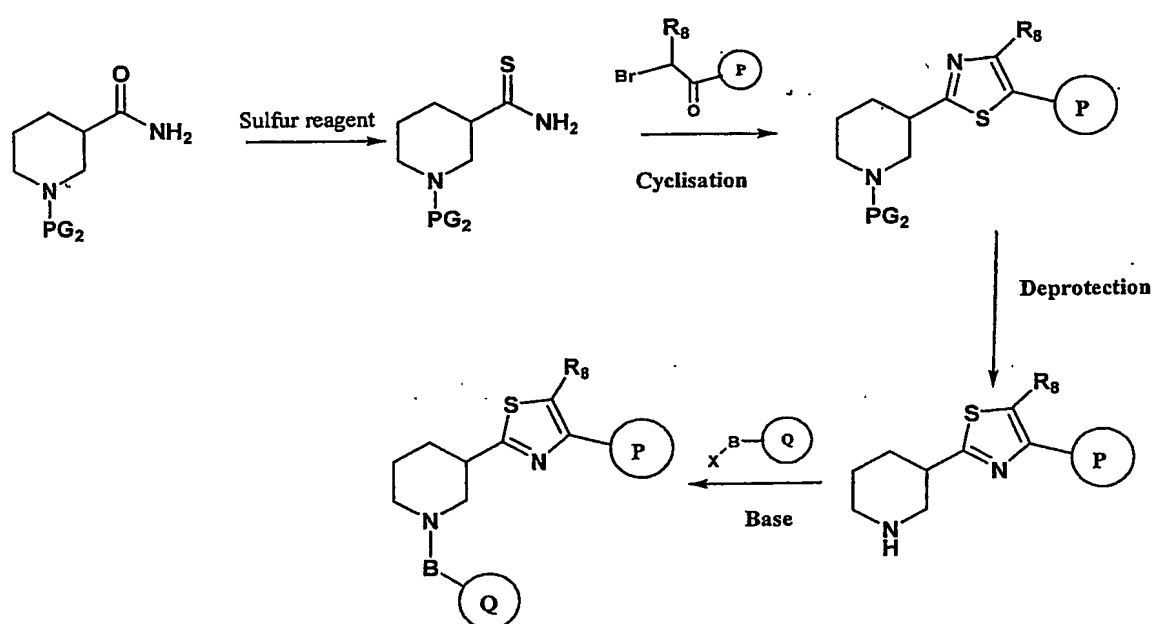
The precursor Aryl-pyrazole derivatives are prepared according to synthetic routes well known in the art (A. R. Katritzky A.R. and C. W. Rees (1984) *Comprehensive Heterocyclic Chemistry*, Pergamon Press).

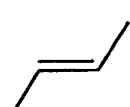
The compounds of formula I-A in the case where A is a group of formula



and W is a 3-substituted piperidine ring may be prepared according to the synthetic sequences illustrated in the Schemes 21.

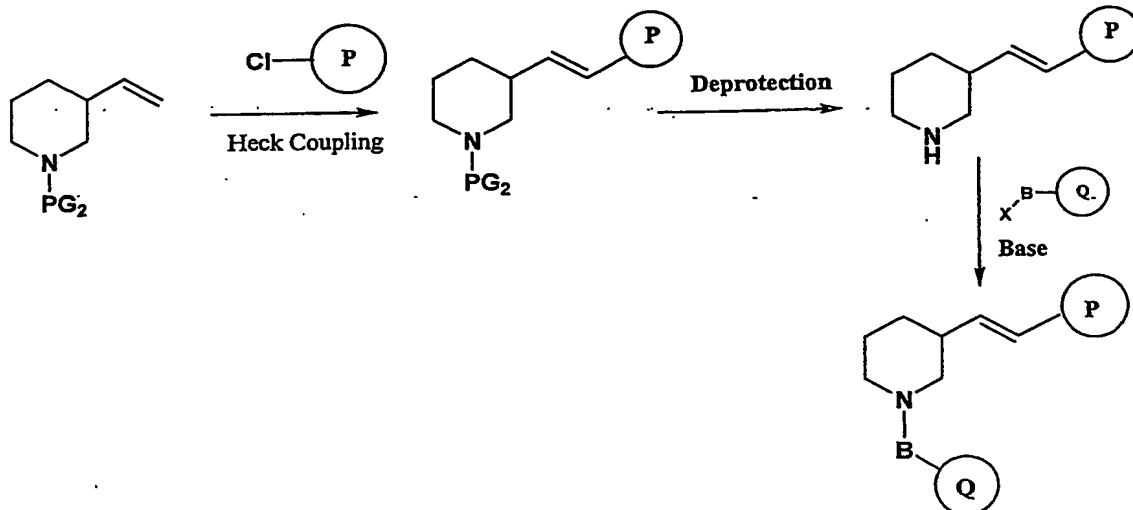
Scheme 21



The compounds of formula I-A in the case where A is a group of formula  and W is a 3-substituted piperidine ring may be prepared according to the synthetic sequences illustrated in the Schemes 22.

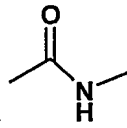
The scheme 22 illustrates the preparation of disubstituted ethylenic derivatives by reacting an protected vinyl piperidine, with a substituted P, for example 1-Fluoro-4-iodo-benzene. Thus in Scheme 5, X includes halides such as Cl, Br, I or trifluoromethanesulfonyl and paratoluenesulfonyl. Such general route of synthesis has been reported in Artzhur D: Brosius and al.; *JACS*. 1999, 121, 700-709.

Scheme 22

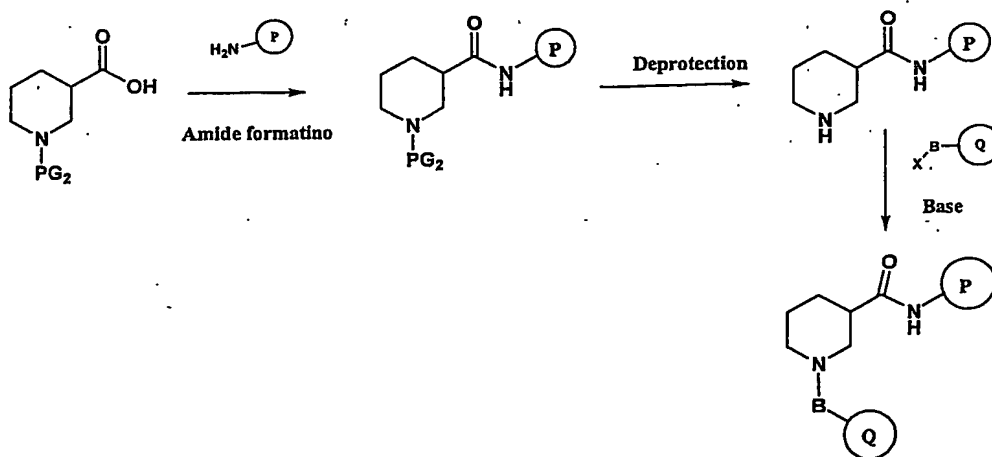


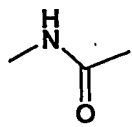
This palladium catalyzed C-C coupling reaction requires a catalyst such as $\text{PdCl}_2(\text{PPh}_3)_2$, $\text{Pd}(\text{PPh}_3)_4$, $\text{Pd}(\text{OAc})_2$ or Pd on carbon in a suitable solvent like DMF, acetonitrile or benzene. Typically a co-catalyst such as copper(I) iodide and a base (e.g., triethylamine, diisopropylamine, potassium acetate...) will also be present in the reaction mixture. The coupling reaction typically proceeds by allowing the reaction temperature to warm slowly from about 0° up to ambient temperature, or heated to a temperature anywhere between 30°C and 150°C . The reaction mixture is then maintained at a suitable temperature for a time in the range of about 1 up to 24 hours, with about 12 hours typically being sufficient. Protecting groups PG_2 are removed using standard methods.

The precursor protected vinyl piperidine derivative is prepared according to synthetic routes well known in the art (see for example Artzhur D: Brosius and al.; *JACS*. 1999, 121, 700-709).

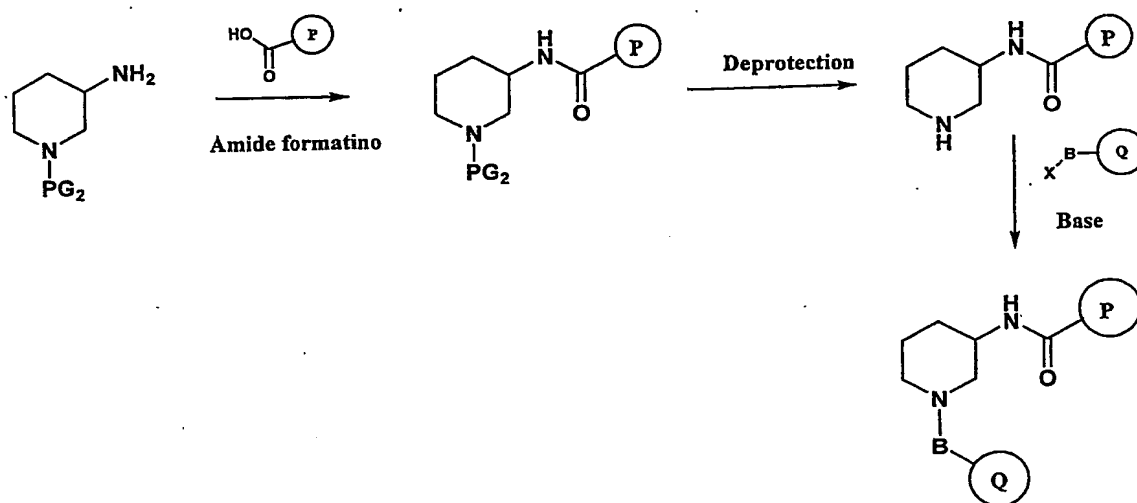
The compounds of formula I-A in the case where A is a group of formula  and W is a 3-substituted piperidine ring may be prepared according to the synthetic sequences illustrated in the Schemes 23.

Scheme 23



The compounds of formula I-A in the case where A is a group of formula  and W is a 3-substituted piperidine ring may be prepared according to the synthetic sequences illustrated in the Schemes 23.

Scheme 24



The compounds of Formula I which are basic in nature can form a wide variety of different pharmaceutically acceptable salts with various inorganic and organic acids. These salts are readily prepared by treating the base compounds with a substantially equivalent amount of the chosen mineral or organic acid in a suitable organic solvent such as methanol, ethanol or isopropanol (see P. Heinrich Stahl, Camille G. Wermuth, *Handbook of Pharmaceuticals Salts, Properties, Selection and Use*, Wiley, 2002).

PHARMACOLOGY:

Some of the compounds of formula I have been tested according to the following methods:

mGluR5 binding assay

Activity of compounds of the invention was examined following a radioligand binding techniques using rat or mouse whole brain and 3-H MPEP or 3H-methoxy methyl MPEP as a ligand following similar methods as described in F. Gasparini et al. Bioorg. Med. Chem Letter 2002, 12, 407-409 and in J.F. Anderson et al., J Pharmacol Exp Thera 2002, 303, 3, 1044-1051.

Ki determinations were made from data obtained from 8 points concentration response curve performed in triplicate. By way of illustration, example 12 was found to show $K_i < 10 \mu\text{M}$ in this assay

Phosphoinositide hydrolysis in rat hippocampal slices

Activity of compounds of the invention was examined following a phosphatidyl inositol hydrolysis assay in rat brain slices from rat pups as described by O'Brien et al. (Mol Pharm 2003).

The compounds tested have no effect by themselves on the basal activity on PI hydrolysis but they shifted the quisqualate- or glutamate-concentration-response curve on PI hydrolysis to the left.

EC50 determinations were made from data obtained from 8 points concentration response curve performed in triplicate for the potentiation of low concentration of quisqualate or glutamate (EC20). By way of illustration, example 12 was found to show $\text{EC}_{50} < 1 \mu\text{M}$ in this assay.

Attenuation of drug-induced deficits in prepulse inhibition

Presentation of a weaker stimulus (termed "prepulse") shortly before to a stronger stimulus reduces the startle reaction to the stronger stimulus. This phenomenon is known as prepulse inhibition (PPI) of startle and is an experimental procedure used to model the sensorimotor gating deficits of psychiatric disorders including schizophrenia (Geyer MA et al. (2001) Psychopharmacology, 156:117-154). Indeed, schizophrenic patients show deficits in the human version of this model. Numerous compounds including NMDA receptors antagonists significantly impair the ability of the prepulse to reduce the startle response. Compounds of the present invention have been shown to attenuate PPI and thus are predicted to be useful as therapeutic agents to treat disorders in which deficits in sensorimotor gating and related cognitive deficits are present.

NMDA antagonist-induced hyperactivity

Antagonists of NMDA receptors increase locomotor activity. This effect is hypothesized to be related to symptoms observed in schizophrenic patients. Thus, NMDA receptor antagonist-induced hyperactivity has been used as a model to test compounds for potential antipsychotic activity (Moghaddam B and Adams BW. (1998). Science 281:1349-1352). Attenuation of NMDA antagonist-induced hyperactivity is predictive of antipsychotic properties of compounds. Compounds of the present invention have been shown to attenuate NMDA antagonist-induced hyperactivity and thus are predicted to be useful as therapeutic agents to treat disorders in which deficits in sensorimotor gating and related cognitive deficits are present.

The following non-limiting examples are intended to illustrate the invention. The physical data given for the compounds exemplified is consistent with the assigned structure of those compounds.

EXAMPLES

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviation may be used in the examples and throughout the specification.

g (grams)	Tr (retention time)
Mg (milligrams)	MeOH (methanol)
ml (millilitres)	MeOH (methanol)
μl (microliters)	Hz (Hertz)
M (molar)	LCMS (Liquid Chromatography Mass Spectrum)
MHz (megahertz)	HPLC (High Pressure Liquid Chromatography)
mmol (millimoles)	NMR (Nuclear Magnetic Reasonance)
Min (minutes)	¹ H (proton)
AcOEt (ethyl acetate)	Na ₂ SO ₄ (sodium sulphate)
K ₂ CO ₃ (potassium carbonate)	MgSO ₄ (magnesium sulphate)
PdCl ₂ (PPh ₃) ₂ (Bis(triphenylphosphine) palladium (II) dichloride)	
CDCl ₃ (deuterated chloroform)	HOBT (1-hydroxybenzotriazole)
EDCl.HCl (1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride)	R.T. (Room Temperature)
EtOH (ethyl alcohol)	NaOH (sodium hydroxide)
% (percent)	h (hour)
DCM (dichloromethane)	HCl (hydrochloric acid)
DIEA (diisopropyl ethyl amine)	n-BuLi (n-butyllithium)

Mp (melting point)

THF (tetrahydrofuran)

All references to brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions are conducted not under an inert atmosphere at room temperature unless otherwise noted.

¹H NMR spectra were recorded on a Bruker 500MHz. Chemical shifts are expressed in parts of million (ppm, δ units). Coupling constants are in units of herts (Hz) Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet).

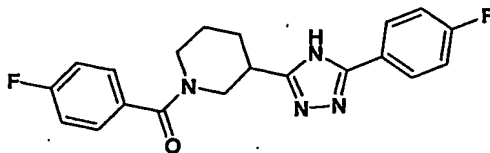
LCMS were recorded on a Waters Micromass ZQ 2996 system by the following conditions. Column 3.0*50mm stainless steel packed with 5 μ m XTerra RP C-18; flow rate 1ml/min; mobile phase: A phase = 0.1% formic acid in water, B phase = 0.07% formic acid in acetonitrile. 0-0.5min (A: 95%, B: 5%), 0.5-6.0min (A: 0%, B: 100%), 6.0-6.5min (A: 95%, B: 5%), 6.5-7min (A: 95%, B: 5%); UV detection Diode Array :200-400nm; Injection volume: 3 μ l.

All mass spectra were taken under electrospray ionisation (ESI) methods.

Most of the reaction were monitored by thin-layer chromatography on 0.25mm Macherey-Nagel silica gel plates (60F-2254), visualized with UV light. Flash column chromatography was performed on silica gel (220-440 mesh, Fluka). Melting point determination was performed on a Buchi B-540 apparatus.

Example 1

(4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-4H-[1,2,4]triazol-3-yl]-piperidin-1-yl}-methanone.



1(A) 1-(4-Fluoro-benzoyl)-piperidine-3-carboxylic acid ethyl ester

To a mixture of Ethyl nipecotate (2 g, 12.72 mmol) in THF (25 ml, 0.5M) was added DIEA (4.79 ml, 27.99 mmol). The reaction mixture was cooled to 0°C and 4-Fluoro-benzoyl chloride (2.5 g – 15.76 mmol) was slowly added. The reaction was to go up to R.T and stirred for 24h. The solution was concentrated and DCM was added following by HCl 1N. The aqueous phase was separated and organic phase was extracted twice with HCl 1N and twice with water, dried over Na₂SO₄, filtered and concentrated to afford 1.15 g (33%) of 1-(4-Fluoro-benzoyl)-piperidine-3-carboxylic acid ethyl ester as a colorless oil which can be used without further purification.

1(B) 1-(4-Fluoro-benzoyl)-piperidine-3-carboxylic acid

1-(4-Fluoro-benzoyl)-piperidine-3-carboxylic acid ethyl ester (1.15 g, 4.42 mmol) was added in a mixture of EtOH/NaOH 3N : 1/1 (8 ml) and the resulting heterogeneous solution was stirred at R.T for 1h. Fuming HCl was added to the mixture until pH = 1. The solution was poured with DCM. The organic layer was separated and the aqueous phase was extracted twice with DCM. The combined organic phase was washed twice with water. The solution was dried over Na₂SO₄, filtered and concentrated to afford 1.13 g (100%) of 1-(4-Fluoro-benzoyl)-piperidine-3-carboxylic acid as an orange oil which can be used without further purification.

1(C) N'-[1-(4-Fluoro-benzoyl)-piperidine-3-carbonyl]-hydrazinecarboxylic acid tert-butyl ester

To a solution of 1-(4-Fluoro-benzoyl)-piperidine-3-carboxylic acid (1.13 g, 4.50 mmol) in DCM (6.5ml) was successively added Hydrazinecarboxylic acid tert-butyl ester (0.59 g, 4.50 mmol), HOBT (0.69 g, 4.50 g) and EDCI.HCl (1.29 g, 6.758 mmol). The mixture was stirred at R.T for 72h. The solvent was removed under reduced pressure and the residue was diluted with DCM was added. The organic layer was washed twice with water, twice with HCl 1N and twice with water. The organic layer was dried over Na₂SO₄, filtered and evaporated to afford 1.19 g (73%) of N'-[1-(4-Fluoro-benzoyl)-piperidine-3-carbonyl]-hydrazinecarboxylic acid tert-butyl ester as a colorless semi-solid.

1(D) 1-(4-Fluoro-benzoyl)-piperidine-3-carboxylic acid hydrazide
N'-[1-(4-Fluoro-benzoyl)-piperidine-3-carbonyl]-hydrazinecarboxylic acid tert-butyl ester was dissolved in 8 ml of 4N HCl (dioxane solution). The resulting reaction mixture was stirred at R.T. for 1h and concentrated to afford 0.88 g (100%) of 1-(4-Fluoro-benzoyl)-piperidine-3-carboxylic acid hydrazide hydrochloride as a white solid.

1(E) (4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-4H-[1,2,4]triazol-3-yl]-piperidin-1-yl}-methanone.

A solution of 4-Fluorobenzonitrile (0.48 g, 4.02 mmol) in methanol (3 ml) was treated with sodium metal (77 mg, 3.5 mmol) and stirred at ambiante temperature for 1h. After this time, the mixture was added to the solution of 1-(4-Fluoro-benzoyl)-piperidine-3-carboxylic acid hydrazide (0.89 g, 3.35 mmol) in methanol (2 ml), and the resulting solution was heated at reflux for 72h.

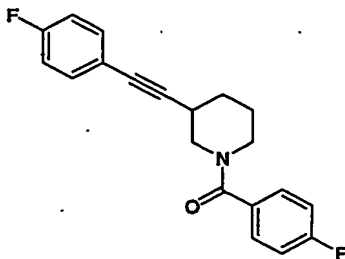
The mixture was concentrated, dissolved in water and neutralized with HCl 1N. The aqueous phase was extracted with DCM, and the organic layer was dried over Na₂SO₄, filtered and concentrated. The purification by reverse phase SPE (water/ACN 45/55) afford 87 mg (7%) of (4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-4H-[1,2,4]triazol-3-yl]-piperidin-1-yl}-methanone as a white solid.

R_f = 0.16 (DCM/MeOH : 98/2); LCMS (Tr) : 3.66min; MS (ES+) gave m/z : 369.2
mp = 95°C;

¹H-NMR (CDCl₃), δ (ppm) : 8.50 (s, NH), 8.05 (m, 2H), 7.52 (m, 2H), 7.15-7.03 (m, 4H), 3.65-3.30 (m, 4H), 2.45 (m, H), 1.85-1.52 (m, 4H).

Example 2

(4-Fluoro-phenyl)-[3-(4-fluoro-phenylethynyl)-piperidin-1-yl]-methanone



2(A) 3-(2,2-Dibromo-vinyl)-piperidine-1-carboxylic acid tert-butyl ester

To a mixture of CBr_4 (1.63 g, 4.92 mmol) and PPh_3 (1.29 g, 4.92 mmol) in DCM (25 ml) was added 1 g (4.69 mmol) 3-Formyl-piperidine-1-carboxylic acid tert-butyl ester (commercially available from Pharmacore) at room temperature. The reaction mixture was stirred at R.T for 24h and the solvent was removed. The crude product was purified by flash chromatography (cyclohexane/AcOEt 90/10) to afford 0.15g (9%) of 3-(2,2-Dibromo-vinyl)-piperidine-1-carboxylic acid tert-butyl ester as a colorless oil.

2(B) 3-Ethynyl-piperidine-1-carboxylic acid tert-butyl ester

To a solution of 3-(2,2-Dibromo-vinyl)-piperidine-1-carboxylic acid tert-butyl ester (0.15 g, 0.42 mmol) in THF (1 ml) was added at -78°C , 0.5 ml of n-BuLi 2.5 M in hexane (1.23 mmol). After 1h at -78°C , the reaction mixture was quenched with 1 ml of water and the aqueous phase was extracted with AcOEt. The combined organic phase was dried over K_2CO_3 , filtered and evaporated to give 80 mg (93%) of 3-Ethynyl-piperidine-1-carboxylic acid tert-butyl ester as a white solid.

2(C) 3-(4-Fluoro-phenylethynyl)-piperidine-1-carboxylic acid tert-butyl ester

To a suspension of CuI (4 mg, 0.02 mmol) in Et_3N (1 ml) was added 3-Ethynyl-piperidine-1-carboxylic acid tert-butyl ester (80 mg, 0.38 mmol) followed by $\text{PdCl}_2(\text{PPh}_3)_2$ (13 mg, 0.02 mmol) and 1-Iodo-4-fluoro-benzene (85 mg, 0.38 mmol). The mixture was stirred 1h at R.T then heated to 60°C for 12h. Et_3N was removed by evaporation. The product was purified by flash chromatography (DCM 100%) to give 0.1 g (89%) of 3-(4-Fluoro-phenylethynyl)-piperidine-1-carboxylic acid tert-butyl ester as a yellow oil.

2(D) 3-(4-Fluoro-phenylethynyl)-piperidine

N'-3-(4-Fluoro-phenylethynyl)-piperidine-1-carboxylic acid tert-butyl ester (80.1 mg, 0.34 mmol) was dissolved in 0.2 ml of 4N HCl (dioxane solution). The resulting reaction mixture was stirred at R.T. for 1h and concentrated to afford 0.14 g (100%) of 3-(4-Fluoro-phenylethynyl)-piperidine hydrochloride as a brown solid.

2(E) (4-Fluoro-phenyl)-[3-(4-fluoro-phenylethynyl)-piperidin-1-yl]-methanone

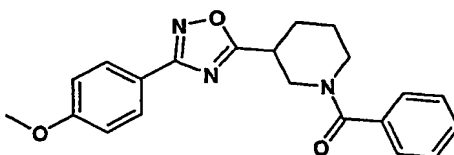
To a mixture of 3-(4-Fluoro-phenylethynyl)-piperidine hydrochloride (0.14 g, 0.58 mmol) in THF (2.3 ml, 0.5M) was added DIEA (0.5 ml, 2.92 mmol). The

reaction mixture was cooled to 0°C and 4-Fluoro-benzoyl chloride (0.139 g – 0.87 mmol) was slowly added. The reaction was to go up to R.T and stirred for 24h. The solution was concentrated and DCM was added following by HCl 1N. The aqueous phase was separated and organic phase was extracted twice with HCl 1N and twice with water, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash chromatography (DCM/MeOH : 98/2) to afford 0.86 mg (45%) of (4-Fluoro-phenyl)-[3-(4-fluoro-phenylethynyl)-piperidin-1-yl]-methanone as a brown oil. R_f = 0.39 (DCM/MeOH : 98/2); LCMS (Tr) : 4.14min; MS (ES+) gave m/z : 326.2 ;

¹H-NMR (CDCl₃), δ (ppm) : 8.10 (d, 2H), 7.60 (d, 2H), 7.15 (d, 2H), 6.94 (d, 2H), 3.47-3.30 (m, 4H), 2.54 (m, H), 1.63-1.50 (m, 4H).

Example 3

{3-[3-(4-Methoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-phenyl-methanone



3(A) N-Hydroxy-4-methoxy-benzamidine

To a mixture of 4-Methoxy-benzonitrile (1.07 g, 8 mmol) and DIEA (4.11 ml, 24 mmol) in EtOH (12.5 ml) was added 1.7 g of Hydroxylamine hydrochloride (24 mmol) and the reaction was heated at 70 °C for 48h. Half of the solvent was removed under reduced pressure. The mixture was poured in DCM (100ml) and water (30ml). 2.5ml of NaOH 1N was added until pH = 9-10. The organic layer was separated and the aqueous phase was extracted with DCM. The organics layers were combined, washed with water, dried over MgSO₄, filtered and evaporated under reduced pressure to afford 1.3 g (98%) of N-Hydroxy-4-methoxy-benzamidine as a colorless oil which can be used without further purification.

3(B) 3-[3-(4-Methoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester

A mixture of N-Hydroxy-4-methoxy-benzamidine (0.20 g, 1.50 mmol), 1-Boc-piperidine-3-carboxylic acid (0.34 g, 1.50 mmol), HOBT (0.23g, 1.50 mmol) and EDCI.HCl (0.43 g, 2.25 mmol) in dioxane (2.5 ml) was stirred at R.T for 7H. After this time the mixture was heated at 80°C overnight with the carousel Radley's. The mixture was concentrated. The organic layer was washed with water, NaOH 1N and water. The organic layer was dried over Na₂SO₄, filtered and evaporated. The crude product was purified by flash chromatography (DCM/MeOH : 99/1) to afford 0.39 mg (72%) of 3-[3-(4-Methoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester as white solid.

3(C) 3-[3-(4-Methoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine

3-[3-(4-Methoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester (0.39 g, 1.08 mmol) was dissolved in 2 ml of 4N HCl (dioxane solution). The resulting reaction mixture was stirred at R.T. for 1h and concentrated to afford 0.320 g (100%) of 3-[3-(4-Methoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine hydrochloride as a brown solid.

3(D) {3-[3-(4-Methoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-phenyl-methanone

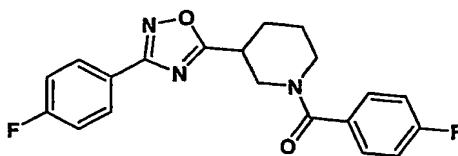
To a mixture of 3-[3-(4-Methoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine hydrochloride (0.320 g, 1.08 mmol) in THF (2.3 ml, 0.5M) was added Pyridine (0.3 ml, 3.78 mmol). The reaction mixture was cooled to 0°C and 4-Fluoro-benzoyl chloride (0.172 g – 0.87 mmol) was slowly added. The reaction was to go up to R.T and stirred for 24h. The solution was concentrated and DCM was added following by HCl 1N. The aqueous phase was separated and organic phase was extracted twice with HCl 1N and twice with water, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash chromatography (DCM/MeOH : 99/1) to afford 0.26 mg (66%) of {3-[3-(4-Methoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-phenyl-methanone as a white powder.

R_f = 0.40 (DCM/MeOH : 99/2); LCMS (Tr) : 4.35min; mp = 121°C; MS (ES+) gave m/z : 364.5 ;

¹H-NMR (CDCl₃), δ (ppm) : 7.95 (d, 2H), 7.51 (m, H), 7.44-7.37 (m, 4H), 6.83 (d, 2H), 3.75 (s, 3H), 3.63-3.34 (m, 4H), 2.48 (m, H), 1.90-1.50 (m, 4H).

Example 4

(4-Fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone



4(A) 3-[3-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester

The compound was prepared following the procedure described in Example 3, using 4-Fluoro-N-hydroxy-benzamidine (commercially available from Aldrich) and the 1-Boc-piperidine-3-carboxylic acid (Yield : 60%)

4(B) 3-[3-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine

The compound was prepared following the procedure described in Example 3, using (Yield : 100%).

4(C) (4-Fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone

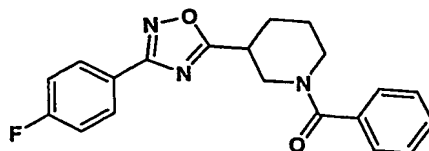
The compound was prepared following the procedure described in Example 3, using 4-Fluoro-benzoyl chloride as the acyl chloride of choice.

Yield : 22%; mp = 118.5-121.5°C (White powder); R_f = 0.30 (DCM/MeOH : 98/2);

LCMS (Tr) : 4.87min; MS (ES+) gave m/z : 370.1 ;
 $^1\text{H-NMR}$ (CDCl_3), δ (ppm) : 8.10 (d, 2H), 7.51 (m, 2H), 7.15-7.0.3 (m, 4H), 3.63-3.34 (m, 4H), 2.48 (m, H), 1.90-1.50 (m, 4H).
 Ana. Calc'd for $\text{C}_{20}\text{H}_{17}\text{F}_2\text{N}_3\text{O}_2$: C, 65.03; H, 4.64; N, 11.38; F, 10.29. Found: C, 64.89; H, 4.75; N, 11.26; F, 10.36.

Example 5

{3-[3-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-phenyl-methanone

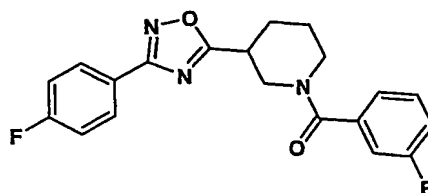


The compound was prepared following the procedure described in Example 3, using 4-Fluoro-benzoyl chloride as the acyl chloride of choice and the 3-[3-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine hydrochloride (already prepared before in Example 4). Yield : 30% (white powder); mp = 82-83°C ; Rf = 0.25 (DCM/MeOH : 98/2);

LCMS (Tr) : 4.70min; MS (ES+) gave m/z : 352.3
 $^1\text{H-NMR}$ (CDCl_3), δ (ppm) : 8.10 (d, 2H), 7.51 (m, 3H), 7.15-7.0.3 (m, 4H), 3.63-3.34 (m, 4H), 2.48 (m, H), 1.90-1.50 (m, 4H).

Example 6

(3-Fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone



The compound was prepared following the procedure described in Example 3, using 3-Fluoro-benzoyl chloride as the acyl chloride of choice and the 3-[3-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine hydrochloride (already prepared before in Example 4).

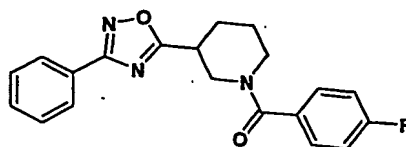
Yield : 42% ; mp = 139-140°C (beige powder); Rf = 0.32 (DCM/MeOH : 98/2);

LCMS (Tr) : 4.87min; MS (ES+) gave m/z : 370.1;

$^1\text{H-NMR}$ (CDCl_3), δ (ppm) : 8.05 (d, 2H), 7.40-7.50 (m, 3H), 7.22-7.00 (m, 3H), 3.65-3.32 (m, 4H), 2.53 (m, H), 1.86-1.45 (m, 4H).

Example 7

(4-Fluoro-phenyl)-[3-(3-phenyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-methanone



7(A) 3-(3-Phenyl-[1,2,4]oxadiazol-5-yl)-piperidine-1-carboxylic acid tert-butyl ester

The compound was prepared following the procedure described in Example 3, using N-hydroxy-benzamidine (commercially available from Maybridge) and the 1-Boc-piperidine-3-carboxylic acid (Yield : 58%).

7(B) 3-(3-Phenyl-[1,2,4]oxadiazol-5-yl)-piperidine

The compound was prepared following the procedure described in Example 3, using (Yield : 94%).

7(C) (4-Fluoro-phenyl)-[3-(3-phenyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-methanone

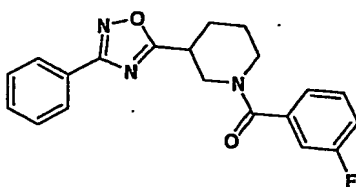
The compound was prepared following the procedure described in Example 3, using 4-Fluoro-benzoyl chloride as the acyl chloride of choice.

Yield : 35% ; mp = 78-79°C (white powder); R_f = 0.24 (DCM/MeOH : 98/2); LCMS (Tr) : 4.75min; MS (ES+) gave m/z : 352.3.

¹H-NMR (CDCl₃), δ (ppm) : 8.10 (d, 2H), 7.48-7.32 (m, 4H), 7.22-7.15 (m, 3H), 3.65-3.32 (m, 4H), 2.53 (m, H), 1.86-1.45 (m, 4H).

Example 8

(3-Fluoro-phenyl)-[3-(3-phenyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-methanone

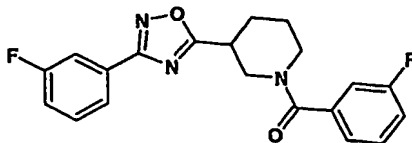


The compound was prepared following the procedure described in Example 3, using 3-Fluoro-benzoyl chloride as the acyl chloride of choice and the 3-(3-Phenyl-[1,2,4]oxadiazol-5-yl)-piperidine hydrochloride (already prepared before in Example 7). Yield : 53% (yellow oil); R_f = 0.25 (DCM/MeOH : 98/2); LCMS (Tr) : 4.77min; MS (ES+) gave m/z : 352.3

¹H-NMR (CDCl₃), σ (ppm) : 8.00-7.72 (m, 2H), 7.48-7.40 (m, 3H), 7.32-7.22 (m, 4H), 3.65-3.32 (m, 4H), 2.53 (m, H), 1.86-1.45 (m, 4H).

Example 9

(3-Fluoro-phenyl)-{3-[3-(3-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone



9(A) N-Hydroxy-3-fluoro-benzamidine

To a mixture of 3-Fluoro-benzonitrile (1.21 g, 10 mmol) and DIEA (5.20 ml, 30 mmol) in EtOH (20 ml) was added 2.08 g of Hydroxylamine hydrochloride (30 mmol) and the reaction was heated at 70 °C for 48h. Half of the solvent was removed under reduced pressure. The mixture was poured in DCM (100ml) and water (30ml). 2.5ml of NaOH 1N was added until pH = 9-10. The organic layer was separated and the aqueous phase was extracted with DCM. The organics layers were combined, washed with water, dried over MgSO₄, filtered and evaporated under reduced pressure to afford 1.48 g (96%) of N-Hydroxy-3-fluoro-benzamidine as a white solid which can be used without further purification.

9(B) 3-[3-(3-Fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester

The compound was prepared following the procedure described in Example 3, using N-Hydroxy-3-fluoro-benzamidine and the 1-Boc-piperidine-3-carboxylic acid (Yield : 78%)

9(C) 3-[3-(3-Fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine

The compound was prepared following the procedure described in Example 3, using (Yield : 96%).

9(D) (3-Fluoro-phenyl)-{3-[3-(3-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone

The compound was prepared following the procedure described in Example 3, using 3-Fluoro-benzoyl chloride as the acyl chloride of choice (Yield : 54%).

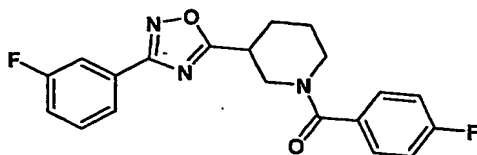
Yield : 53% (yellow oil); R_f = 0.31 (DCM/MeOH : 98/2); LCMS (Tr) : 4.88min;

MS (ES+) gave m/z : 370.3;

¹H-NMR (CDCl₃), δ (ppm) : 7.96-7.72 (m, 2H), 7.66 (m, H), 7.42-7.30 (m, 2H), 7.30-7.25 (m, 2H), 7.00 (m, 1H), 3.65-3.32 (m, 4H), 2.53 (m, H), 1.86-1.45 (m, 4H).

Example 10

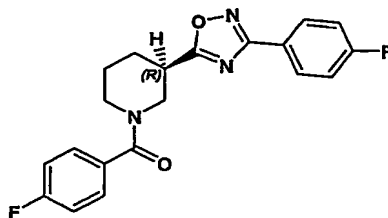
(4-Fluoro-phenyl)-{3-[3-(3-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone



The compound was prepared following the procedure described in Example 3, using 4-Fluoro-benzoyl chloride as the acyl chloride of choice and the 3-[3-(3-Fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine hydrochloride (already prepared before in Example 9). Yield : 50% (yellow oil); Mp = 86-89°C (beige powder); R_f = 0.28 (DCM/MeOH : 98/2); LCMS (Tr) : 4.88min; MS (ES⁺) gave m/z : 370.3; ¹H-NMR (CDCl₃), δ (ppm) : 8.05-7.90 (m, 2H), 7.30-7.23 (m, 2H), 7.25-7.15 (m, 3H), 7.00 (m, 1H), 3.65-3.32 (m, 4H), 2.53 (m, H), 1.86-1.45 (m, 4H).

Example 11

R-(4-Fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone



11(A) *R*-3-[3-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester

The compound was prepared following the procedure described in Example 3, using 4-Fluoro-N-hydroxy-benzamidine (commercially available from Aldrich) and the *R*-1-Boc-piperidine-3-carboxylic acid (Yield : 79%)

11(B) *R*-3-[3-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine

The compound was prepared following the procedure described in Example 3, using (Yield : 68%).

11(C) *R*-(4-Fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone

The compound was prepared following the procedure described in Example 4, using 4-Fluoro-benzoyl chloride as the acyl chloride of choice.

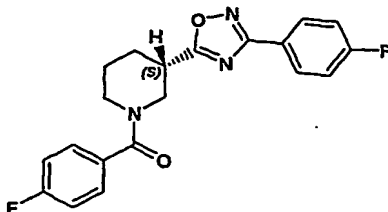
Yield : 28%; mp = 98°C (White powder); R_f = 0.30 (DCM/MeOH : 98/2);

LCMS (Tr) : 4.87min; MS (ES⁺) gave m/z : 370.1;

¹H-NMR (CDCl₃), δ (ppm) : 8.05 (d, 2H), 7.48 (m, 2H), 7.15-7.03 (m, 4H), 3.63-3.34 (m, 4H), 2.48 (m, H), 1.90-1.50 (m, 4H).

Example 12

S-(4-Fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone



12(A) *S*-3-[3-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine-1-carboxylic acid tert-butyl ester

The compound was prepared following the procedure described in Example 3, using 4-Fluoro-*N*-hydroxy-benzamidine (commercially available from Aldrich) and the *S*-1-Boc-piperidine-3-carboxylic acid (Yield : 84%)

12(B) *S*-3-[3-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidine

The compound was prepared following the procedure described in Example 3, using (Yield : 63%).

12(B) *S*-(4-Fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone

The compound was prepared following the procedure described in Example 4, using 4-Fluoro-benzoyl chloride as the acyl chloride of choice.

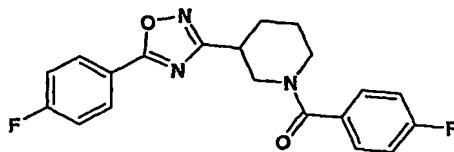
Yield : 51%; mp = 99°C (White powder); R_f = 0.30 (DCM/MeOH : 98/2);

[α]_D²⁰ = + 103° (c=1, CHCl₃); LCMS (Tr) : 4.87min; MS (ES⁺) gave m/z : 370.1

¹H-NMR (CDCl₃), δ (ppm) : 8.05 (d, 2H), 7.48 (m, 2H), 7.15-7.0.3 (m, 4H), 3.63-3.34 (m, 4H), 2.48 (m, H), 1.90-1.50 (m, 4H).

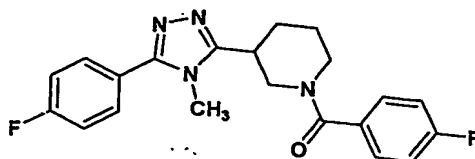
Example 13

(4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone



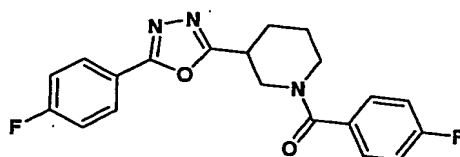
Example 14

(4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-piperidin-1-yl}-methanone



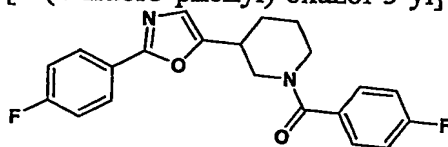
Example 15

(4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-piperidin-1-yl}-methanone



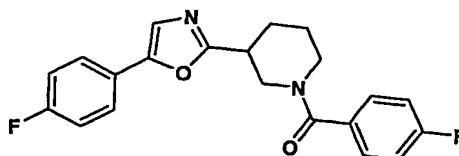
Example 16

(4-Fluoro-phenyl)-{3-[2-(4-fluoro-phenyl)-oxazol-5-yl]-piperidin-1-yl}-methanone



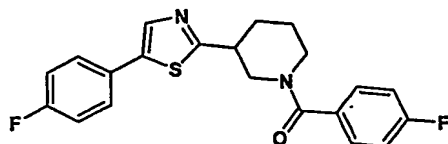
Example 17

(4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-oxazol-2-yl]-piperidin-1-yl}-methanone



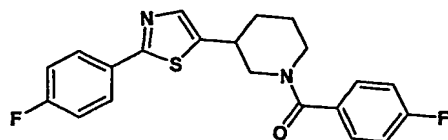
Example 18

(4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-thiazol-2-yl]-piperidin-1-yl}-methanone



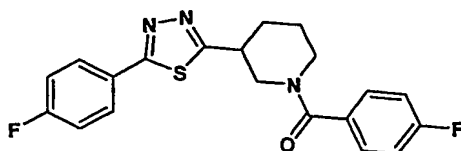
Example 19

(4-Fluoro-phenyl)-{3-[2-(4-fluoro-phenyl)-thiazol-5-yl]-piperidin-1-yl}-methanone



Example 20

(4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-[1,3,4]thiadiazol-2-yl]-piperidin-1-yl}-methanone



Typical examples of recipes for the formulation of the invention are as follows:

1) Tablets

Compound of the example 12	5 to 50 mg
Di-calcium phosphate	20 mg
Lactose	30 mg
Talcum	10 mg
Magnesium stearate	5 mg
Potato starch	ad 200 mg

In this example, the compound of the example 12 can be replaced by the same amount of any of the described examples 1 to 12.

2) Suspension:

An aqueous suspension is prepared for oral administration so that each 1 milliliter contains 1 to 5 mg of one of the described example, 50 mg of sodium carboxymethyl cellulose, 1 mg of sodium benzoate, 500 mg of sorbitol and water ad 1 ml.

3) Injectable

A parenteral composition is prepared by stirring 1.5 % by weight of active ingredient of the invention in 10% by volume propylene glycol and water.

4) Ointment

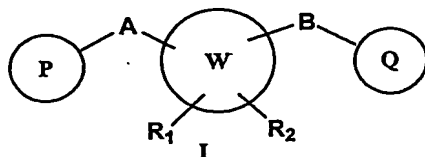
Compound of the example 12	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
White petroleum	15 g
Water	ad 100 g

In this example, the compound 12 can be replaced by the same amount of any of the described examples 1 to 20.

Reasonable variations are not to be regarded as a departure from the scope of the invention. It will be obvious that the thus described invention may be varied in many ways by those skilled in the art.

Claims:

1. A compound which conforms to the general formula I:

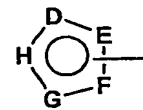
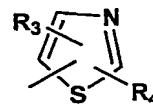
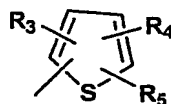
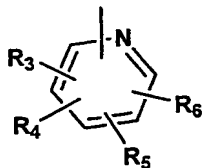
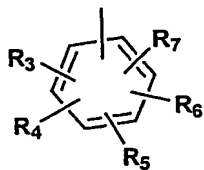


Wherein

W represents a 5 to 7 atoms cycloalkyl or heterocycloalkyl ring.

R₁ and R₂ represent independently hydrogen, C₁-C₆-alkyl, C₁-C₆-alkenyl, C₁-C₆-alkynyl, arylalkyl, heteroarylalkyl, hydroxy, amino, aminoalkyl, hydroxyalkyl, C₁-C₆-alkoxy or R₁ and R₂ together can form a C₃-C₇-cycloalkyl ring, a carbonyl bond C=O or a carbon double bond.

P and Q are each independently selected and denote an aryl or heteroaryl group of formula



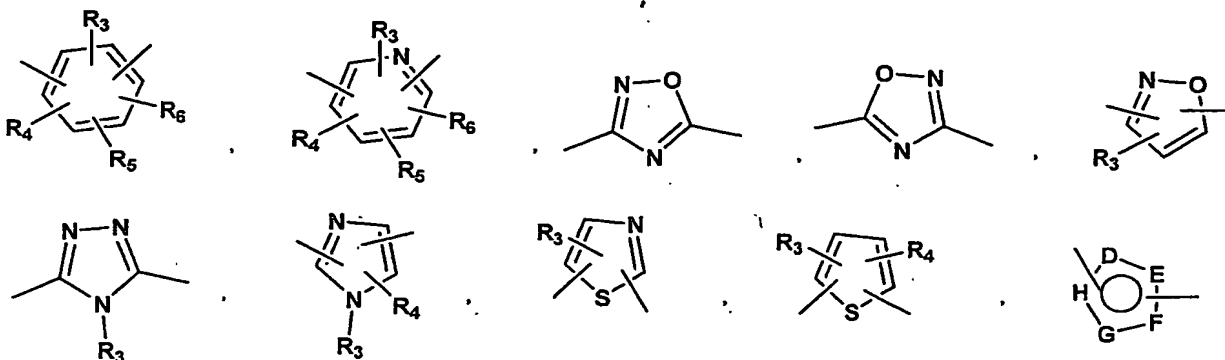
R₃, R₄, R₅, R₆, and R₇ independently are hydrogen, halogen, -CN, nitro, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₃-C₇-cycloalkylalkyl, C₁-C₆-alkenyl, C₁-C₆-alkynyl, halo-C₁-C₆-alkyl, heteroaryl, heteroarylalkyl, arylalkyl, aryl, -OR₈, -NR₈R₉, -C(=NR₁₀)NR₈R₉, N(=NR₁₀)NR₈R₉, -NR₈COR₉, NR₈CO₂R₉, NR₈SO₂R₉, -NR₁₀CO NR₈R₉, -SR₈, -S(=O)R₈, -S(=O)₂R₈, -S(=O)₂NR₈R₉, -C(=O)R₈, -C(=O)₂R₈, -C(=O)NR₈R₉, -C(=NR₈)R₉, or C(=NOR₈)R₉ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic aryl or heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, -CN, C₁-C₆-alkyl, -O(C₀-C₆-alkyl), -O(C₃-C₇-cycloalkylalkyl), -O(aryl), -O(heteroaryl), -O(C₁-C₃-alkylaryl), -O(C₁-C₃-alkylheteroaryl), -N(C₀-C₆-alkyl)(C₀-C₃-alkylaryl) or -N(C₀-C₆-alkyl)(C₀-C₃-alkylheteroaryl) groups;

R₈, R₉, R₁₀ each independently is hydrogen, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₃-C₇-cycloalkylalkyl, -C₆-alkenyl, C₁-C₆-alkynyl, halo-C₁-C₆-alkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, C₁-C₆-alkyl, -O(C₀-C₆-alkyl), -O(C₃-C₇-cycloalkylalkyl), -O(aryl), -O(heteroaryl), -N(C₀-C₆-alkyl)(C₀-C₆-alkyl), -N(C₀-C₆-alkyl)(C₃-C₇-cycloalkyl) or -N(C₀-C₆-alkyl)(aryl) substituents;

D, E, F, G and H represent independently $-C(R_3)=$, $-C(R_3)=C(R_4)-$, $-C(=O)-$, $-C(=S)-$, $-O-$, $-N=$, $-N(R_3)-$ or $-S-$.

A

is azo $-N=N-$, ethyl, ethenyl, ethynyl, $-NR_8C(=O)-$, $NR_8S(=O)_2-$, $-C(=O)NR_8-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-S(=O)_2NR_8-$, $-C(=O)-O-$, $-O-C(=O)-$, $-C(=NR_8)NR_9-$, $C(=NOR_8)NR_9-$, $-NR_8C(=NOR_9)-$, $=N-O-$, $-O-N=CH-$ or a group aryl or heteroaryl of formula



R_3 , R_4 , R_5 and R_6 independently are as defined above.

D, E, F, G and H independently are as defined above.

B

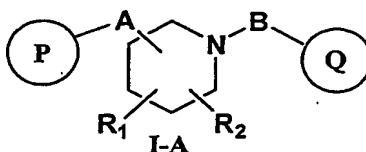
represents a single bond, $-C(=O)-C_0-C_2$ -alkyl-, $C(=O)-O-$, $-C(=O)NR_8-C_0-C_2$ -alkyl-, $-C(=NR_8)NR_9-S(=O)-C_0-C_2$ -alkyl-, $-S(=O)_2-C_0-C_2$ -alkyl-, $-S(=O)_2NR_8-C_0-C_2$ -alkyl-, $C(=NR_8)-C_0-C_2$ -alkyl-, $-C(=NOR_8)-C_0-C_2$ -alkyl- or $-C(=NOR_8)NR_9-C_0-C_2$ -alkyl-;

R_8 and R_9 , independently are as defined above.

Any N may be an N-oxide.

or a pharmaceutically acceptable salt, hydrate or solvate of such compound.

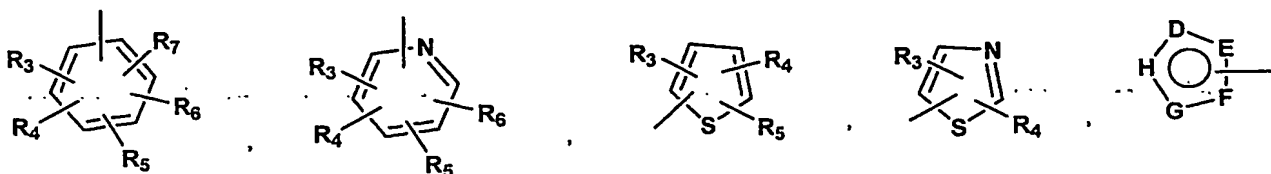
2. A compound according to claim 1 having the formula I-A



Wherein

R_1 and R_2 represent independently hydrogen, C_1-C_6 -alkyl, C_1-C_6 -alkenyl, C_1-C_6 -alkynyl, arylalkyl, heteroarylalkyl, hydroxy, amino, aminoalkyl, hydroxyalkyl, C_1-C_6 -alkoxy or R_1 and R_2 together can form a C_3-C_7 -cycloalkyl ring, a carbonyl bond $C=O$ or a carbon double bond.

P and Q are each independently selected and denote an aryl or heteroaryl group of formula



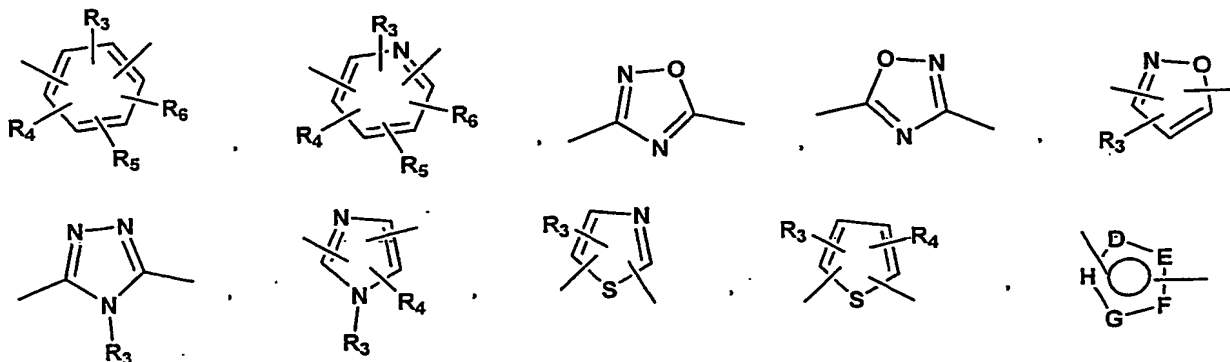
R_3 , R_4 , R_5 , R_6 , and R_7 independently are hydrogen, halogen, -CN, nitro, C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl, C_3 - C_7 -cycloalkylalkyl, C_1 - C_6 -alkenyl, C_1 - C_6 -alkynyl, halo- C_1 - C_6 -alkyl, -heteroaryl, heteroarylalkyl, arylalkyl, aryl, -OR₈, -NR₈R₉, -C(=NR₁₀)NR₈R₉, N(=NR₁₀)NR₈R₉, -NR₈COR₉, NR₈CO₂R₉, NR₈SO₂R₉, -NR₁₀CO NR₈R₉, -SR₈, -S(=O)R₈, -S(=O)₂R₈, -S(=O)₂NR₈R₉, -C(=O)R₈, -C(=O)₂R₈, -C(=O)NR₈R₉, -C(=NR₈)R₉, or C(=NOR₈)R₉ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic aryl or heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, -CN, C_1 - C_6 -alkyl, -O(C_0 - C_6 -alkyl), -O(C_3 - C_7 -cycloalkylalkyl), -O(aryl), -O(heteroaryl), -O(C_1 - C_3 -alkylaryl), -O(C_1 - C_3 -alkylheteroaryl), -N(C_0 - C_6 -alkyl)(C_0 - C_3 -alkylaryl) or -N(C_0 - C_6 -alkyl)(C_0 - C_3 -alkylheteroaryl) groups;

R_8 , R_9 , R_{10} each independently is hydrogen, C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl, C_3 - C_7 -cycloalkylalkyl, - C_6 -alkenyl, C_1 - C_6 -alkynyl, halo- C_1 - C_6 -alkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, C_1 - C_6 -alkyl, -O(C_0 - C_6 -alkyl), -O(C_3 - C_7 -cycloalkylalkyl), -O(aryl), -O(heteroaryl), -N(C_0 - C_6 -alkyl)(C_0 - C_6 -alkyl), -N(C_0 - C_6 -alkyl)(C_3 - C_7 -cycloalkyl) or -N(C_0 - C_6 -alkyl)(aryl) substituents;

D, E, F, G and H represent independently -C(R_3)=, -C(R_3)=C(R_4)-, -C(=O)-, -C(=S)-, -O-, -N=, -N(R_3)- or -S-.

A

is azo -N=N-, ethyl, ethenyl, ethynyl, -NR₈C(=O)-, NR₈S(=O)₂-, -C(=O)NR₈-, -S-, -S(=O)-, -S(=O)₂-, -S(=O)₂NR₈-, -C(=O)-O-, -O-C(=O)-, -C(=NR₈)NR₉-, C(=NOR₈)NR₉-, -NR₈C(=NOR₉)-, =N-O-, -O-N=CH- or a group aryl or heteroaryl of formula



R_3 , R_4 , R_5 and R_6 independently are as defined above.

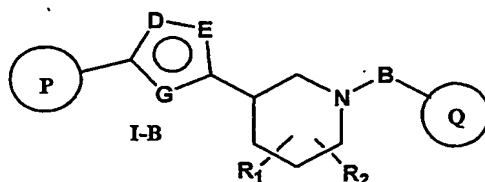
D, E, F, G and H independently are as defined above.

B - represents a single bond, $-C(=O)-C_0-C_2\text{-alkyl-}$, $-C(=O)-O-$, $-C(=O)NR_8-$, $-C_0-C_2\text{-alkyl-}$, $-C(=NR_8)NR_9-S(=O)-C_0-C_2\text{-alkyl-}$, $-S(=O)_2-C_0-C_2\text{-alkyl-}$, $-S(=O)_2NR_8-C_0-C_2\text{-alkyl-}$, $-C(=NR_8)-C_0-C_2\text{-alkyl-}$, $-C(=NOR_8)-C_0-C_2\text{-alkyl-}$ or $-C(=NOR_8)NR_9-C_0-C_2\text{-alkyl-}$;
 R_8 and R_9 , independently are as defined above.

Any N may be an N-oxide.

or a pharmaceutically acceptable salt, hydrate or solvate of such compound.

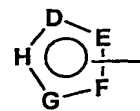
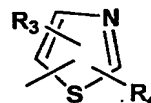
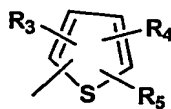
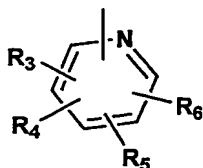
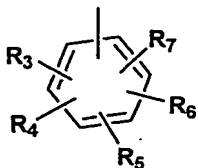
3. A compound according to claim 1 or 2 having the formula I-B



Wherein

R_1 and R_2 represent independently hydrogen, $C_1-C_6\text{-alkyl}$, $C_1-C_6\text{-alkenyl}$, $C_1-C_6\text{-alkynyl}$, arylalkyl, heteroarylalkyl, hydroxy, amino, aminoalkyl, hydroxyalkyl, $C_1-C_6\text{-alkoxy}$ or R_1 and R_2 together can form a $C_3-C_7\text{-cycloalkyl}$ ring, a carbonyl bond $C=O$ or a carbon double bond.

P and Q are each independently selected and denote an aryl or heteroaryl group of formula



R_3 , R_4 , R_5 , R_6 , and R_7 independently are hydrogen, halogen, $-CN$, nitro, $C_1-C_6\text{-alkyl}$, $C_3-C_6\text{-cycloalkyl}$, $C_3-C_7\text{-cycloalkylalkyl}$, $C_1-C_6\text{-alkenyl}$, $C_1-C_6\text{-alkynyl}$, halo- $C_1-C_6\text{-alkyl}$, heteroaryl, heteroarylalkyl, arylalkyl, aryl, $-OR_8$, $-NR_8R_9$, $-C(=NR_{10})NR_8R_9$, $N(=NR_{10})NR_8R_9$, $-NR_8COR_9$, $NR_8CO_2R_9$, $NR_8SO_2R_9$, $-NR_{10}CO\ NR_8R_9$, $-SR_8$, $-S(=O)R_8$, $-S(=O)_2R_8$, $-S(=O)_2NR_8R_9$, $-C(=O)R_8$, $-C(=O)_2R_8$, $-C(=O)NR_8R_9$, $-C(=NR_8)R_9$, or $C(=NOR_8)R_9$ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic aryl or heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, $-CN$, $C_1-C_6\text{-alkyl}$, $-O(C_0-C_6\text{-alkyl})$, $-O(C_3-C_7\text{-cycloalkylalkyl})$, $-O(\text{aryl})$, $-O(\text{heteroaryl})$, $-O(C_1-C_3\text{-alkylaryl})$, $-O(C_1-C_3\text{-alkylheteroaryl})$, $-N(C_0-C_6\text{-alkyl})(C_0-C_3\text{-alkylaryl})$ or $-N(C_0-C_6\text{-alkyl})(C_0-C_3\text{-alkylheteroaryl})$ groups;

R_8, R_9, R_{10} each independently is hydrogen, C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl, C_3 - C_7 -cycloalkylalkyl, $-C_6$ -alkenyl, C_1 - C_6 -alkynyl, halo- C_1 - C_6 -alkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, $-CN$, C_1 - C_6 -alkyl, $-O(C_0$ - C_6 -alkyl), $-O(C_3$ - C_7 -cycloalkylalkyl), $-O(aryl)$, $-O(heteroaryl)$, $-N(C_0$ - C_6 -alkyl)(C_0 - C_6 -alkyl), $-N(C_0$ - C_6 -alkyl)(C_3 - C_7 -cycloalkyl) or $-N(C_0$ - C_6 -alkyl)(aryl) substituents;

D, E, F, G and H represent independently $-C(R_3)=$, $-C(R_3)=C(R_4)-$, $-C(=O)-$, $-C(=S)-$, $-O-$, $-N=$, $-N(R_3)-$ or $-S-$.

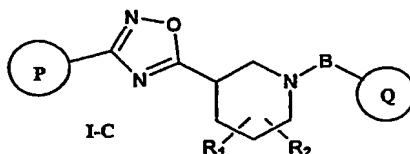
D, E and G are independently as defined above.

B represents a single bond, $-C(=O)-C_0$ - C_2 -alkyl-, $C(=O)-O-$, $-C(=O)NR_8$ - C_0 - C_2 -alkyl-, $-C(=NR_8)NR_9-S(=O)-C_0$ - C_2 -alkyl-, $-S(=O)_2-C_0$ - C_2 -alkyl-, $-S(=O)_2NR_8-C_0$ - C_2 -alkyl-, $C(=NR_8)-C_0$ - C_2 -alkyl-, $-C(=NOR_8)-C_0$ - C_2 -alkyl- or $-C(=NOR_8)NR_9-C_0$ - C_2 -alkyl-;
 R_8 and R_9 , independently are as defined above.

Any N may be an N-oxide.

or a pharmaceutically acceptable salt, hydrate or solvate of such compound.

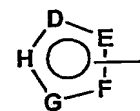
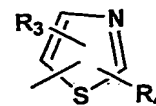
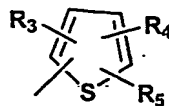
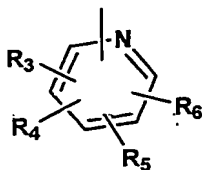
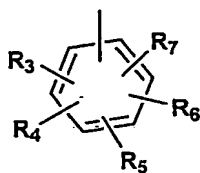
4. A compound according to claim 1 or 2 having the formula I-C



Wherein

R_1 and R_2 represent independently hydrogen, C_1 - C_6 -alkyl, C_1 - C_6 -alkenyl, C_1 - C_6 -alkynyl, arylalkyl, heteroarylalkyl, hydroxy, hydroxyalkyl, C_1 - C_6 -alkoxy or R_1 and R_2 together can form a carbonyl bond $C=O$ or a carbon double bond.

P and Q are each independently selected and denote an aryl or heteroaryl group of formula



R_3, R_4, R_5, R_6 , and R_7 independently are hydrogen, halogen, $-CN$, nitro, C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl, C_3 - C_7 -cycloalkylalkyl, C_1 - C_6 -alkenyl, C_1 - C_6 -alkynyl, halo- C_1 - C_6 -alkyl, heteroaryl, heteroarylalkyl, arylalkyl, aryl, $-OR_8$, $-NR_8R_9$, $-C(=NR_{10})NR_8R_9$, $N(=NR_{10})NR_8R_9$, $-NR_8COR_9$,

$\text{NR}_8\text{CO}_2\text{R}_9$, $\text{NR}_8\text{SO}_2\text{R}_9$, $-\text{NR}_{10}\text{CO NR}_8\text{R}_9$, $-\text{SR}_8$, $-\text{S}(=\text{O})\text{R}_8$, $-\text{S}(=\text{O})_2\text{R}_8$, $-\text{S}(=\text{O})_2\text{NR}_8\text{R}_9$, $-\text{C}(=\text{O})\text{R}_8$, $-\text{C}(=\text{O})_2\text{R}_8$, $-\text{C}(=\text{O})\text{NR}_8\text{R}_9$, $-\text{C}(=\text{NR}_8)\text{R}_9$, or $\text{C}(=\text{NOR}_8)\text{R}_9$ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic aryl or heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, $-\text{CN}$, $\text{C}_1\text{-C}_6\text{-alkyl}$, $-\text{O}(\text{C}_0\text{-C}_6\text{-alkyl})$, $-\text{O}(\text{C}_3\text{-C}_7\text{-cycloalkylalkyl})$, $-\text{O}(\text{aryl})$, $-\text{O}(\text{heteroaryl})$, $-\text{O}(\text{C}_1\text{-C}_3\text{-alkylaryl})$, $-\text{O}(\text{C}_1\text{-C}_3\text{-alkylheteroaryl})$, $-\text{N}(\text{C}_0\text{-C}_6\text{-alkyl})(\text{C}_0\text{-C}_3\text{-alkylaryl})$ or $-\text{N}(\text{C}_0\text{-C}_6\text{-alkyl})(\text{C}_0\text{-C}_3\text{-alkylheteroaryl})$ groups;

R_8 , R_9 , R_{10} each independently is hydrogen, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_3\text{-C}_6\text{-cycloalkyl}$, $\text{C}_3\text{-C}_7\text{-cycloalkylalkyl}$, $-\text{C}_6\text{-alkenyl}$, $\text{C}_1\text{-C}_6\text{-alkynyl}$, halo- $\text{C}_1\text{-C}_6\text{-alkyl}$, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, $-\text{CN}$, $\text{C}_1\text{-C}_6\text{-alkyl}$, $-\text{O}(\text{C}_0\text{-C}_6\text{-alkyl})$, $-\text{O}(\text{C}_3\text{-C}_7\text{-cycloalkylalkyl})$, $-\text{O}(\text{aryl})$, $-\text{O}(\text{heteroaryl})$, $-\text{N}(\text{C}_0\text{-C}_6\text{-alkyl})(\text{C}_0\text{-C}_6\text{-alkyl})$, $-\text{N}(\text{C}_0\text{-C}_6\text{-alkyl})(\text{C}_3\text{-C}_7\text{-cycloalkyl})$ or $-\text{N}(\text{C}_0\text{-C}_6\text{-alkyl})(\text{aryl})$ substituents;

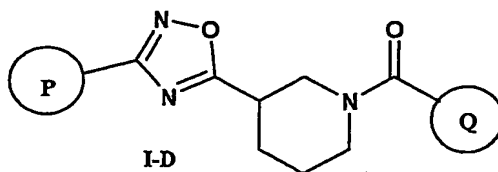
D, E, F, G and H represent independently $-\text{C}(\text{R}_3)=$, $-\text{C}(\text{R}_3)=\text{C}(\text{R}_4)-$, $-\text{C}(=\text{O})-$, $-\text{C}(=\text{S})-$, $-\text{O}-$, $-\text{N}=$, $-\text{N}(\text{R}_3)-$ or $-\text{S}-$.

B represents a single bond, $-\text{C}(=\text{O})-\text{C}_0\text{-C}_2\text{-alkyl}-$, $\text{C}(=\text{O})-\text{O}-$, $-\text{C}(=\text{O})\text{NR}_8-\text{C}_0\text{-C}_2\text{-alkyl}-$, $-\text{C}(=\text{NR}_8)\text{NR}_9-\text{S}(=\text{O})-\text{C}_0\text{-C}_2\text{-alkyl}-$, $-\text{S}(=\text{O})_2-\text{C}_0\text{-C}_2\text{-alkyl}-$, $-\text{S}(=\text{O})_2\text{NR}_8-\text{C}_0\text{-C}_2\text{-alkyl}-$, $\text{C}(=\text{NR}_8)-\text{C}_0\text{-C}_2\text{-alkyl}-$, $-\text{C}(=\text{NOR}_8)-\text{C}_0\text{-C}_2\text{-alkyl}-$ or $-\text{C}(=\text{NOR}_8)\text{NR}_9-\text{C}_0\text{-C}_2\text{-alkyl}-$; R_8 and R_9 , independently are as defined above.

Any N may be an N-oxide.

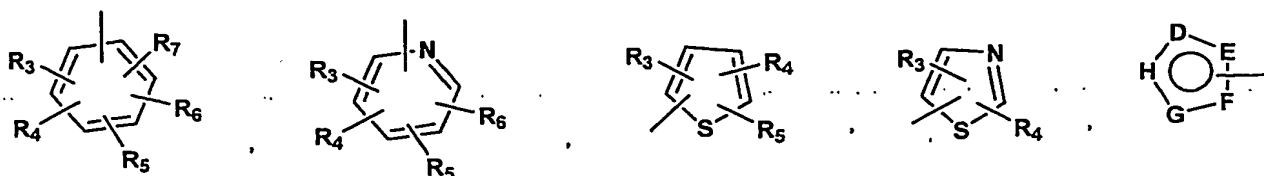
or a pharmaceutically acceptable salt, hydrate or solvate of such compound.

4. A compound according to claim 1 or 2 having the formula I-D



Wherein

P and Q are each independently selected and denote an aryl or heteroaryl group of formula



$R_3, R_4, R_5, R_6,$ and R_7 independently are hydrogen, halogen, $-\text{CN}$, nitro, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_3\text{-C}_6\text{-cycloalkyl}$, $\text{C}_3\text{-C}_7\text{-cycloalkylalkyl}$, $\text{C}_1\text{-C}_6\text{-alkenyl}$, $\text{C}_1\text{-C}_6\text{-alkynyl}$, halo- $\text{C}_1\text{-C}_6\text{-alkyl}$, heteroaryl, heteroarylalkyl, arylalkyl, aryl, $-\text{OR}_8$, $-\text{NR}_8\text{R}_9$, $-\text{C}(=\text{NR}_{10})\text{NR}_8\text{R}_9$, $\text{N}(=\text{NR}_{10})\text{NR}_8\text{R}_9$, $-\text{NR}_8\text{COR}_9$, $\text{NR}_8\text{CO}_2\text{R}_9$, $\text{NR}_8\text{SO}_2\text{R}_9$, $-\text{NR}_{10}\text{CO NR}_8\text{R}_9$, $-\text{SR}_8$, $-\text{S}(=\text{O})\text{R}_8$, $-\text{S}(=\text{O})_2\text{R}_8$, $-\text{S}(=\text{O})_2\text{NR}_8\text{R}_9$, $-\text{C}(=\text{O})\text{R}_8$, $-\text{C}(=\text{O})_2\text{R}_8$, $-\text{C}(=\text{O})\text{NR}_8\text{R}_9$, $-\text{C}(=\text{NR}_8)\text{R}_9$, or $\text{C}(=\text{NOR}_8)\text{R}_9$ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic aryl or heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, $-\text{CN}$, $\text{C}_1\text{-C}_6\text{-alkyl}$, $-\text{O}(\text{C}_0\text{-C}_6\text{-alkyl})$, $-\text{O}(\text{C}_3\text{-C}_7\text{-cycloalkylalkyl})$, $-\text{O}(\text{aryl})$, $-\text{O}(\text{heteroaryl})$, $-\text{O}(\text{C}_1\text{-C}_3\text{-alkylaryl})$, $-\text{O}(\text{C}_1\text{-C}_3\text{-alkylheteroaryl})$, $-\text{N}(\text{C}_0\text{-C}_6\text{-alkyl})(\text{C}_0\text{-C}_3\text{-alkylaryl})$ or $-\text{N}(\text{C}_0\text{-C}_6\text{-alkyl})(\text{C}_0\text{-C}_3\text{-alkylheteroaryl})$ groups;

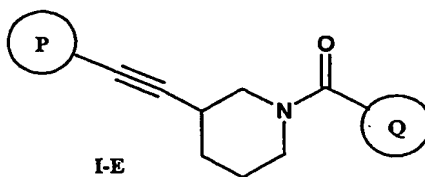
R_8, R_9, R_{10} each independently is hydrogen, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_3\text{-C}_6\text{-cycloalkyl}$, $\text{C}_3\text{-C}_7\text{-cycloalkylalkyl}$, $\text{C}_6\text{-alkenyl}$, $\text{C}_1\text{-C}_6\text{-alkynyl}$, halo- $\text{C}_1\text{-C}_6\text{-alkyl}$, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, $-\text{CN}$, $\text{C}_1\text{-C}_6\text{-alkyl}$, $-\text{O}(\text{C}_0\text{-C}_6\text{-alkyl})$, $-\text{O}(\text{C}_3\text{-C}_7\text{-cycloalkylalkyl})$, $-\text{O}(\text{aryl})$, $-\text{O}(\text{heteroaryl})$, $-\text{N}(\text{C}_0\text{-C}_6\text{-alkyl})(\text{C}_0\text{-C}_6\text{-alkyl})$, $-\text{N}(\text{C}_0\text{-C}_6\text{-alkyl})(\text{C}_3\text{-C}_7\text{-cycloalkyl})$ or $-\text{N}(\text{C}_0\text{-C}_6\text{-alkyl})(\text{aryl})$ substituents;

$\text{D}, \text{E}, \text{F}, \text{G}$ and H represent independently $-\text{C}(\text{R}_3)=$, $-\text{C}(\text{R}_3)=\text{C}(\text{R}_4)-$, $-\text{C}(=\text{O})-$, $-\text{C}(=\text{S})-$, $-\text{O}-$, $-\text{N}=$, $-\text{N}(\text{R}_3)-$ or $-\text{S}-$.

Any N may be an N -oxide.

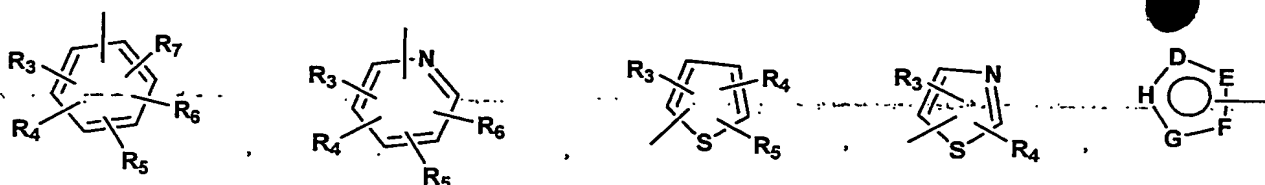
or a pharmaceutically acceptable salt, hydrate or solvate of such compound.

6. A compound according to claim 1 or 2 having the formula I-E



Wherein

P and Q are each independently selected and denote an aryl or heteroaryl group of formula



R_3 , R_4 , R_5 , R_6 , and R_7 independently are hydrogen, halogen, -CN, nitro, C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl, C_3 - C_7 -cycloalkylalkyl, C_1 - C_6 -alkenyl, C_1 - C_6 -alkynyl, halo- C_1 - C_6 -alkyl, heteroaryl, heteroarylalkyl, arylalkyl, aryl, -OR₈, -NR₈R₉, -C(=NR₁₀)NR₈R₉, N(=NR₁₀)NR₈R₉, -NR₈COR₉, NR₈CO₂R₉, NR₈SO₂R₉, -NR₁₀CO NR₈R₉, -SR₈, -S(=O)R₈, -S(=O)₂R₈, -S(=O)₂NR₈R₉, -C(=O)R₈, -C(=O)₂R₈, -C(=O)NR₈R₉, -C(=NR₈)R₉, or C(=NOR₈)R₉ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic aryl or heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, -CN, C_1 - C_6 -alkyl, -O(C_0 - C_6 -alkyl), -O(C_3 - C_7 -cycloalkylalkyl), -O(aryl), -O(heteroaryl), -O(C_1 - C_3 -alkylaryl), -O(C_1 - C_3 -alkylheteroaryl), -N(C_0 - C_6 -alkyl)(C_0 - C_3 -alkylaryl) or -N(C_0 - C_6 -alkyl)(C_0 - C_3 -alkylheteroaryl) groups;

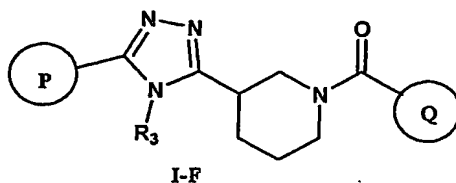
R_8 , R_9 , R_{10} each independently is hydrogen, C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl, C_3 - C_7 -cycloalkylalkyl, - C_6 -alkenyl, C_1 - C_6 -alkynyl, halo- C_1 - C_6 -alkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, C_1 - C_6 -alkyl, -O(C_0 - C_6 -alkyl), -O(C_3 - C_7 -cycloalkylalkyl), -O(aryl), -O(heteroaryl), -N(C_0 - C_6 -alkyl)(C_0 - C_6 -alkyl), -N(C_0 - C_6 -alkyl)(C_3 - C_7 -cycloalkyl) or -N(C_0 - C_6 -alkyl)(aryl) substituents;

D, E, F, G and H represent independently -C(R₃)=, -C(R₃)=C(R₄)-, -C(=O)-, -C(=S)-, -O-, -N=, -N(R₃)- or -S-.

Any N may be an N-oxide.

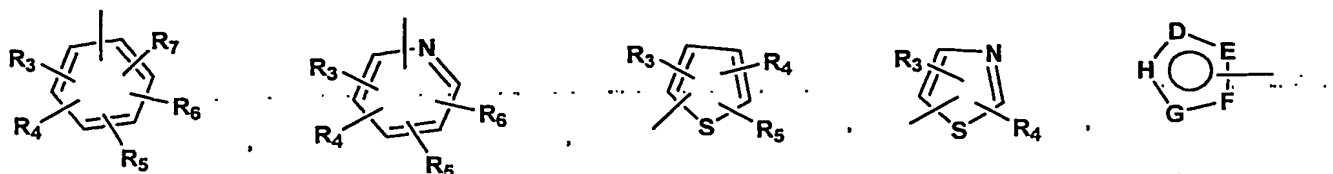
or a pharmaceutically acceptable salt, hydrate or solvate of such compound.

7. A compound according to claim 1 or 2 having the formula I-F



Wherein

P and Q are each independently selected and denote an aryl or heteroaryl group of formula



$R_3, R_4, R_5, R_6,$ and R_7 independently are hydrogen, halogen, -CN, nitro, C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl, C_3 - C_7 -cycloalkylalkyl, C_1 - C_6 -alkenyl, C_1 - C_6 -alkynyl, halo- C_1 - C_6 -alkyl, heteroaryl, heteroarylalkyl, arylalkyl, aryl, -OR₈, -NR₈R₉, -C(=NR₁₀)NR₈R₉, N(=NR₁₀)NR₈R₉, -NR₈COR₉, NR₈CO₂R₉, NR₈SO₂R₉, -NR₁₀CO NR₈R₉, -SR₈, -S(=O)R₈, -S(=O)₂R₈, -S(=O)₂NR₈R₉, -C(=O)R₈, -C(=O)₂R₈, -C(=O)NR₈R₉, -C(=NR₈)R₉, or C(=NOR₈)R₉ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic aryl or heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, -CN, C_1 - C_6 -alkyl, -O(C_0 - C_6 -alkyl), -O(C_3 - C_7 -cycloalkylalkyl), -O(aryl), -O(heteroaryl), -O(C_1 - C_3 -alkylaryl), -O(C_1 - C_3 -alkylheteroaryl), -N(C_0 - C_6 -alkyl)(C_0 - C_3 -alkylaryl) or -N(C_0 - C_6 -alkyl)(C_0 - C_3 -alkylheteroaryl) groups;

R_8, R_9, R_{10} each independently is hydrogen, C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl, C_3 - C_7 -cycloalkylalkyl, - C_6 -alkenyl, C_1 - C_6 -alkynyl, halo- C_1 - C_6 -alkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, C_1 - C_6 -alkyl, -O(C_0 - C_6 -alkyl), -O(C_3 - C_7 -cycloalkylalkyl), -O(aryl), -O(heteroaryl), -N(C_0 - C_6 -alkyl)(C_0 - C_6 -alkyl), -N(C_0 - C_6 -alkyl)(C_3 - C_7 -cycloalkyl) or -N(C_0 - C_6 -alkyl)(aryl) substituents;

D, E, F, G and H represent independently -C(R₃)=, -C(R₃)=C(R₄)-, C(=O)-, -C(=S)-, -O-, -N=, -N(R₃)- or -S-.

Any N may be an N-oxide.

or a pharmaceutically acceptable salt, hydrate or solvate of such compound.

8. A compound according to claims 1 to 7, which can exist as optical isomers, wherein said compound is either the racemic mixture or an individual optical isomer.

9. A compound according to claims 1 to 8, wherein said compounds are selected from:

{3-[3-(4-Methoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-phenyl-methanone
 {3-[3-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-phenyl-methanone
 (4-Fluoro-phenyl)-[3-(3-phenyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-methanone
 (3-Fluoro-phenyl)-[3-(3-phenyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-methanone

(4-Fluoro-phenyl)-{3-[3-(3-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone
 (3-Fluoro-phenyl)-{3-[3-(3-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone
 (4-Fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone
 (3-Fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone
 (4-Fluoro-phenyl)-[3-(4-fluoro-phenylethynyl)-piperidin-1-yl]-methanone
 (4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-4H-[1,2,4]triazol-3-yl]-piperidin-1-yl}-methanone
 (*R*)-(4-Fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone
 (*S*)-(4-Fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone
 (4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
 (4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-piperidin-1-yl}-methanone
 (4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-piperidin-1-yl}-methanone
 (4-Fluoro-phenyl)-{3-[2-(4-fluoro-phenyl)-oxazol-5-yl]-piperidin-1-yl}-methanone
 (4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-oxazol-2-yl]-piperidin-1-yl}-methanone
 (4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-thiazol-2-yl]-piperidin-1-yl}-methanone
 (4-Fluoro-phenyl)-{3-[2-(4-fluoro-phenyl)-thiazol-5-yl]-piperidin-1-yl}-methanone
 (4-Fluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-[1,3,4]thiadiazol-2-yl]-piperidin-1-yl}-methanone

10. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claims 1 to 9 and a pharmaceutically acceptable carriers and/or excipients.

11. A use or method of treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR5 allosteric modulators, comprising administering to a mammal in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 10.

12. A use or method of treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR5 positive allosteric modulators (enhancers), comprising administering to a mammal in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 10.

13. A use or method useful for treating or preventing central nervous system disorders selected from the group consisting of anxiety disorders: Agoraphobia, Generalized Anxiety Disorder (GAD), Obsessive-Compulsive Disorder (OCD), Panic Disorder, Posttraumatic Stress Disorder (PTSD), Social Phobia, Other Phobias, Substance-Induced Anxiety Disorder, comprising administering an effective amount of a compound/composition according to claims 1 to 10.

14. A use or method useful for treating or preventing central nervous system disorders selected from the group consisting of childhood disorders: Attention-Deficit/Hyperactivity Disorder), comprising administering an effective amount of a compound/composition according to claims 1 to 10.

15. A use or method useful for treating or preventing central nervous system disorders selected from the group consisting of eating Disorders (Anorexia Nervosa, Bulimia Nervosa), comprising administering an effective amount of a compound/composition according to claims 1 to 10.

16. A use or method useful for treating or preventing central nervous system disorders selected from the group consisting of mood disorders: Bipolar Disorders (I & II), Cyclothymic Disorder, Depression, Dysthymic Disorder, Major Depressive Disorder, Substance-Induced Mood Disorder, comprising administering an effective amount of a compound/composition according to claims 1 to 10.

17. A use or method useful for treating or preventing central nervous system disorders selected from the group consisting of psychotic disorders: Schizophrenia, Delusional Disorder, Schizoaffective Disorder, Schizophreniform Disorder, Substance-Induced Psychotic Disorder, comprising administering an effective amount of a compound/composition according to claims 1 to 10.

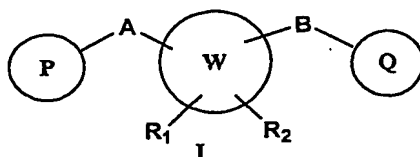
18. A use or method useful for treating or preventing central nervous system disorders selected from the group consisting of cognitive disorders: Delirium, Substance-Induced Persisting Delirium, Dementia, Dementia Due to HIV Disease, Dementia Due to Huntington's Disease, Dementia Due to Parkinson's Disease, Dementia of the Alzheimer's Type, Substance-Induced Persisting Dementia, Mild Cognitive Impairment, comprising administering an effective amount of a compound/composition according to claims 1 to 10.

19. A use or method useful for treating or preventing central nervous system disorders selected from the group consisting of personality disorders: Obsessive-Compulsive Personality Disorder, Schizoid, Schizotypal disorder, comprising administering an effective amount of a compound/composition according to claims 1 to 10.

20. A use or method useful for treating or preventing central nervous system disorders selected from the group consisting of substance-related disorders: Alcohol abuse, Alcohol dependence, Alcohol withdrawal, Alcohol withdrawal delirium, Alcohol-induced psychotic disorder, Amphetamine dependence, Amphetamine withdrawal, Cocaine dependence, Cocaine withdrawal, Nicotine dependence, Nicotine withdrawal, Opioid dependence, Opioid withdrawal, comprising administering an effective amount of a compound/composition according to claims 1 to 10.

21. A use or method according to any of claims 11 to 20, wherein the mGluR5 modulator has an EC50 of 1 μ M or less.

Abstract: the present invention relates to new compounds of formula (I) wherein A, B, P, Q, W, R₁ and R₂ are defined in the description; invention compounds are useful in the prevention or treatment of central nervous system disorders as well as other disorders modulated by mGluR5 receptors.



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